Internet-based cognitive behavioural therapy for patients with rheumatoid arthritis

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CHAPTER 1

General introduction

Introduction

When people are confronted with a chronic somatic condition, they are faced with psychological and social adjustment, in addition to the physical and medical difficulties [1, 2]. People are resilient and most patients adjust successfully, yet about a third of patients struggle with psychological adjustment in daily life [3-5]. Psychological treatment, and in particular cognitive behavioural therapy (CBT), has been shown to be effective in reducing symptoms common to chronic somatic conditions [e.g. 6-8], such as fatigue [e.g. 9,10], pain [e.g.11-14], and anxiety and depressive symptoms [e.g.15-19]. CBT is defined as a structured, present-oriented psychological therapy directed toward solving current problems and teaching clients skills to modify dysfunctional thinking and behaviour [20]. Although research provides sufficient grounds to incorporate CBT in standard multidisciplinary healthcare for patients, this is not yet the case [8, 18, 21]. Often mentioned barriers include the unavailability of trained specialized therapists, travel inconvenience for patients to attend regular treatment sessions, and costs of healthcare in general [22-24]. In light of these barriers, a solution has been sought using the technological possibilities of the internet as a vehicle of implementation. Benefits include flexibility for the patient and therapist, assumed cost reductions, and potential efficiency in terms of time reduction [25-27].

In the past decade, the body of research on internet-based psychological interventions has been growing. Early studies of internet-based psychological treatment and specifically internet-based cognitive behavioural treatment (ICBT) have been promising in terms of both feasibility and effectiveness [26-29]. Studies within the field of mental health care have shown that therapist time is reduced [30] and treatment can be effective in reducing symptoms [30, 31]. Preliminary evidence concerning cost-related aspects has also shown that internet-based treatment may be a cost-effective solution [32]. The body of research in the

area of chronic somatic conditions is still scarce. Results that have been found need to be replicated, and the heterogeneity of the current published studies limit the overall conclusions that can be drawn [28, 33, 34]. The current thesis aims to describe the current state of the art on internet-based cognitive behavioural therapy (ICBT) for patients with chronic somatic conditions, explores specific topics related to internet-based psychological treatment, such as patient preferences and therapist guidance, and presents the results of a randomized controlled trial (RCT) into the (cost-) effectiveness of an ICBT intervention for patients with rheumatoid arthritis in particular.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is defined as a chronic inflammatory autoimmune disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [35]. Prevalence of RA is estimated at about 0.5 – 1% in Europe and Northern America [36]. In the past decades, the management of RA has been enhanced through the optimal use of disease-modifying anti rheumatic drugs (DMARDS) and the availability of biologic agents, resulting in drastically improved clinical outcomes [37, 38]. Despite these clinical improvements, patients generally experience a reduced quality of life as compared to healthy people [39-41]. A chronic somatic condition such as RA requires patient adjustment [2, 40, 42-44]. Adjustments include taking medication, handling disease-related symptoms such as pain and fatigue, and finding a balance between insufficient or an overload of activity, which may exacerbate symptoms of joint stiffness and fatigue or inflammation. Several reviews have shown that the majority of patients are capable to successfully cope with their RA, but similar to other chronic somatic conditions about a third of patients have long-term adjustment problems. These problems are characterized by, for example, negative mood, anxiety, pain, fatigue and a large impact of the disease on daily life [40, 45, 46]. Patients with RA on average experience more

psychological symptoms such as anxiety and negative mood than healthy individuals [47-49]. Social well-being is also influenced, for example in the context of social activities [50, 51], but also in the societal context, for example due to a potential negative impact on one's work ability [52-54]. Furthermore, psychosocial symptoms and physical symptoms interact. Increased physical symptoms exacerbate psychosocial symptoms such as anxiety and depression [48, 55] and psychosocial symptoms have been shown to predict poorer outcome in terms of disease activity, pain and fatigue [56-59]. This thesis is mainly aimed at RA, although the problems experiences are also common to other chronic somatic conditions such as psoriasis. Part of the studies also report on patients with psoriasis, which is a chronic immune-mediated inflammatory skin condition typically characterized by red and scaly plaques on the skin [60]. Patients with psoriasis often experience itch, alongside similar symptoms which are experienced by patients with RA, such as fatigue and psychosocial problems [61].

Internet-based cognitive behavioural treatment for patients with RA

Psychological treatment has received extensive attention within the domain of RA. Several reviews and meta-analyses have shown psychological treatment and specifically cognitive behavioural treatments to be effective in reducing physical symptoms such as pain and fatigue [46, 62], psychological aspects such as depressive symptoms [40, 63], and social aspects such as enhancing social well-being [64]. Aside from beneficial effects on disease-related symptoms, general treatment adherence and ultimately management of RA can be positively influenced by cognitive behavioural treatment [65-68]. Even though these previous reviews have mentioned certain limitations of the existing literature and provided suggestions for future research, such as a need for high quality studies and extensive research into which treatment aspects are especially relevant to patients, evidence is in favor of incorporating CBT into the management of patients with RA [69].

Within the domain of RA, the internet and internet-based technologies have been applied to a small degree in the past decade, for example to monitor disease activity [70], for patient education [71-73], and for encouragement of physical activity [74]. A few trials have reported on outcomes of psychological strategies to enhance self-management within RA by means of internet-based technologies [75-77]. Patients were offered educational modules to enhance self-efficacy and self-management, and either no support was given [76] or weekly telephone calls to encourage use of the intervention [75] or support by peer moderators [77]. All trials reported enhancement of self-efficacy and beneficial effects on specific outcomes. As there are currently too few trials on ICBT in RA to meaningfully summarize the evidence, we conducted a systematic review and meta-analysis on the effectiveness of ICBT in a variety of chronic somatic conditions on general and specific disease-related outcomes. This review and meta-analysis provides a comprehensive overview of the current evidence base and future needs in this area (Chapter 2).

Internet-based cognitive behavioural treatment: challenges and potential solutions

Even though internet-based treatment holds promise for the future, important challenges are also reported. The main challenges are related to dissemination of and adherence to the interventions. In regard to dissemination, challenges are related to generalizing the uptake of internet-based interventions, which are currently predominantly being used among relatively high educated women and patients with relatively high levels of self-efficacy [78]. Rates of non-adherence vary widely and can be as high as eighty percent [79-81], possibly limiting the intended reach and outcome of the intervention. To further dissemination and improve adherence, several suggestions have been offered that could provide solutions to these challenges. First, patient views should be taken into account from the developmental stage to ensure a good fit of the intervention with the specific needs and expectations of the

target population [82, 83]. Second, as therapist guidance often has been positively related to outcomes [30, 84, 85], incorporating some degree of guidance could enhance treatment effectiveness. Third, tailoring the intervention to patient treatment goals and specific characteristics may increase adherence, because patients may feel more committed to attain their own goals as opposed to general treatment goals and feel more comfortable with assignments attuned to their own needs [79, 82, 86].

Patient preferences

A first step toward attaining a higher feasibility of internet-based intervention may be to involve patients from early stages of intervention development. As the users of the interventions, patients bring unique views on the acceptability of new interventions and are able to put forward important ideas on how engagement may be enhanced [86, 87] .Their knowledge of the disease and experiences with aspects such as the healthcare system may aid in shaping treatment optimally to patient needs. Within the domain of rheumatology, a relevant example is provided by the patient involvement imbedded within Outcome Measures in Rheumatology (OMERACT), where patient research partners are incorporated in the structure of the organization and contribute to the development of core sets of outcome measures [88].

Within the domain of internet-based interventions, the patient perspective is often evaluated after participation in, and often completion of, the intervention [89]. Therefore, feasibility of these interventions may be limited to patients who have some degree of computer literacy and self-efficacy [90]. Yet, when patients' ideas and suggestions regarding internet-based interventions would be known prior to the intervention development, this may be used to optimally connect the intervention to the intended population and be beneficial for the intervention uptake [91]. In order to determine which possible advantages and

disadvantages of internet-based psychological treatments patients with RA or the chronic inflammatory skin disease psoriasis endorse, a telephone-based survey was conducted in these patient groups (Chapter 3).

Therapeutic guidance

The role of therapeutic guidance during internet-based interventions has been emphasized as a possible predictor of intervention outcomes, adherence and drop-out prevention [92-95]. With regard to outcomes, within face-to-face psychological treatments a sound therapeutic relationship has been positively related to treatment effects [96-98]. Of three frequently assessed aspects of the therapeutic relationship; agreement on treatment goals, agreement on treatment strategies, and the degree of feeling a bond, especially the first two have been found to lead to stronger effects of the interventions on outcomes [98]. Within the domain of internet-based interventions, the role of therapeutic guidance for the effect of the intervention on outcomes is not yet clear [92, 99]. The main conclusion of a review on the therapeutic relationship during internet-based treatments was that too few data are available to draw any firm conclusions on the relationship between therapeutic guidance and effects, although the reviewed papers generally showed support for the establishment and maintenance of the therapeutic relationship during the interventions [92]. In addition several meta-analyses and reviews have shown that therapist-guided internet-based interventions have less drop-out and higher adherence rates compared to self-help internet-based interventions without guidance [26, 30, 89, 100].

In order to gain more insight into the relevance of the therapeutic relationship during internet-based interventions, it needs to be measured adequately. Up to date, measures used in face-to-face treatments have also been used to measure the quality of the therapeutic relationship in internet-based interventions [92, 101, 102]. Yet, the internet environment of

this type of treatment offers particular challenges as well as potential benefits that may influence the therapeutic relationship. For example, in internet-based interventions, there is often a time-lapse between the messages that are sent between patient and therapist. For patients who benefit from the time to reflect on their reply and taking the time to write down their feelings, this may be a specific advantage. It is relevant to measure these specific internet-based characteristics related to the therapeutic relationship. Ultimately, such a questionnaire could aid in clarifying the role of therapist guidance in internet-based interventions and the role of guidance in the prediction of outcomes of internet-based interventions. Therefore, an internet-specific therapeutic relationship questionnaire was developed and validated (Chapter 4) and reported on as part of two case reports (Chapter 5).

Tailoring treatments

Another route towards increased effectiveness and engagement of patients during internet-based interventions is the tailoring of the interventions to individual patients needs and characteristics [40, 82, 103-105]. There are several ways to tailor an internet-based intervention. One way is to specify which target population would be most likely to benefit from the intervention and only invite these patients to partake in the intervention [40, 82]. Another way is to encourage patients to formulate their own goals and incorporate these goals into the internet-based intervention, for example by enabling patients to write these down on the homepage of the intervention [82, 106, 107]. Setting personal goals and it's positive link to motivation has been studied for decades [108, 109]. Yet another possible way to tailor the internet-based intervention is to take specific patient characteristics into account to determine the specific patient's content of the intervention, as not all assignments and parts of the intervention may be relevant to all patients [82]. Receiving irrelevant treatment facets may frustrate patients and could possibly be one reason for intervention non-adherence [81, 105, 110]. As part of personalized healthcare, a one-size-fits-all approach may

therefore need to be replaced by tailoring internet-based treatments to specific patient characteristics and goals [3, 82, 105].

In order to know more on how tailoring can be included in internet-based interventions and which parts of the intervention are essential for its effects, information on the content of internet-based interventions is needed. Although the guidelines of reporting on internet-based interventions increasingly recommend a detailed description of the interventions [90], this often remains rather limited. Resultantly, most publications to date lack specific information on the active role of patients during the internet-based intervention [111] and the degree to which a patient received a standardized treatment package or could choose certain intervention aspects [27, 29, 104]. Also, the type of therapist guidance often remains unclear [34, 92]. Because the main papers on an RCT often lack the space to extensively describe the intervention in detail, the reporting of single case reports allow researchers and clinicians more insight into the contents of an intervention . This form of reporting allows for the description of the intervention and the intended outcomes in the light of a treatment trajectory of one or two specific patients. The value of case reports for clinical practice and research has recently been outlined and consensus guidelines are provided in support [112, 113]. Consequently, two case reports of a therapist-guided and tailored ICBT for patients with chronic somatic conditions, including RA, are included in this thesis (Chapter 5).

Effectiveness of therapist-guided and tailored internet-based cognitive behavioural therapy in rheumatoid arthritis.

Although case reports are a step toward more knowledge on the content and potential effectiveness of ICBT for patients with RA, its actual effectiveness preferably needs to be demonstrated in a RCT within a larger patient group. Based on an effective therapist-guided and tailored face-to-face CBT intervention [114], an ICBT intervention was developed and

examined in patients with RA in order to foster implementation into daily practice. Incorporating the previously mentioned aspects of tailoring and therapist guidance, the intervention was targeted specifically at patients with elevated levels of distress, which holds for about one-third of patients with RA [114-116].

To evaluate the intervention, we conducted an RCT in patients with RA with heightened levels of distress to examine the effectiveness of such an intervention on a comprehensive set of outcome domains, including psychological and physical functioning and impact on daily life (Chapter 6).

Cost-effectiveness

For ICBT to be likely to be implemented in clinical practice, not only its effectiveness, but also its cost-effectiveness should be studied [117, 118]. Internet-based psychological treatment is often deemed cost-effective due to aspects of reduced travel time, efficiency for both patient and therapist and relatively low costs for development [118, 119]. Some studies on cost-effectiveness have been published [119]; a review within the domain of mental health did indicate that most studies indeed showed cost-effectiveness of the internet-based intervention [118]. However, there is a lack of research on cost-effectiveness in the area of chronic somatic conditions, including patients with rheumatoid arthritis [118, 119].

Within the domain of RA, cost-effectiveness of treatment strategies has received considerable attention, as the use of biologic agents has driven up costs of disease management [120]. However, for psychological interventions little is known on costs in relation to benefits. The few study outcomes pertaining to costs are related to work-related variables, which have shown to be positively influenced by psychological treatment strategies [121]. Also, some studies have found that psychological factors are related to treatment adherence and

treatment outcome; therefore, enhancing psychological well-being may also enhance treatment outcome and cost-effectiveness in the long-term [122]. However, ICBT interventions for patients with RA have not yet been reported on with regard to costs to society. Therefore, alongside the RCT, a cost-effectiveness study of the tailored guided internet-based intervention for patients with RA with elevated levels of distress has been conducted from a societal perspective, comparing the costs and effects with standard rheumatological care as it is currently standard practice in the Netherlands (Chapter 7), in order to obtain information on the potential for dissemination and implementation of ICBT in regular care for patients with RA.

Content of this thesis

This thesis reports on a number of studies conducted to obtain more insight into the potential of ICBT for patients with chronic somatic conditions, with a specific focus on RA. In Chapter 2, the current state of the literature on internet-based treatments for patients with chronic somatic conditions is described by means of a systematic review and meta-analysis. To gain a better insight into the feasibility of ICBT within chronic somatic patient populations, including RA, in Chapter 3 a study is reported on patient preferences for internet-based treatments in patients with RA and psoriasis. Due to the specific character of internet-based interventions as compared to face-to-face treatments in the light of the therapeutic relationship, Chapter 4 describes the development and validation of a questionnaire to specifically measure the internet-based therapeutic relationship.

Based on an effective and disease-generic face-to-face CBT and incorporating the knowledge derived from the previous studies, an internet-based tailored and therapist-guided cognitive behavioural treatment for patients with RA with elevated levels of distress was developed and examined by means of an RCT as an adjunct to standard rheumatological care. To

provide insight into the content of the intervention, Chapter 5 presents two case studies of one patient with RA and one patient with psoriasis. The effectiveness and cost-effectiveness of the RCT in patients with RA are subsequently described in Chapter 6 and Chapter 7, respectively.

The final two chapters of this thesis contain a summary of the findings of the different studies (Chapter 8) and discuss the findings across studies and their implications for research and practice (Chapter 9).

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CHAPTER 2

Internet-Based Cognitive Behavioural Therapy for Patients with Chronic Somatic Conditions: A Meta-Analytic Review.

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Abstract

Background

Patients with chronic somatic conditions face unique challenges accessing mental health care outside of their homes due to symptoms and physical limitations. Internet-based cognitive behavioural therapy (ICBT) has shown to be effective for various psychological conditions. The increasing number of recent trials needs to be systematically evaluated and quantitatively analyzed to determine whether ICBT is also effective for chronic somatic conditions and to gain insight into the types of problems that could be targeted.

Objective

Our goal was to describe and evaluate the effectiveness of guided ICBT interventions for chronic somatic conditions on general psychological outcomes, disease-related physical outcomes, and disease-related impact on daily life outcomes. The role of treatment length was also examined.

Methods

PubMed, PsycINFO, and Embase were searched from inception until February 2012, by combining search terms indicative of effect studies, internet, and cognitive behavioural therapy. Studies were included if they fulfilled the following six criteria: (1) randomized controlled trial, (2) internet-based interventions, (3) based on cognitive behavioural therapy, (4) therapist-guided, (5) adult (≥ 18 years old) patients with an existing chronic somatic condition, and (6) published in English. Twenty-three randomized controlled trials of guided ICBT were selected by two independent raters after reviewing 4848 abstracts. Demographic, clinical, and methodological variables were extracted. Standardized mean differences were

calculated between intervention and control conditions for each outcome and pooled using random effects models when appropriate.

Results

Guided ICBT was shown to improve all outcome categories with small effect sizes for general psychological outcomes (effect size range 0.17 to 0.21) and occasionally larger effects for disease-specific physical outcomes (effect size range -0.04 to 1.19) and disease-related impact outcomes (effect size range 0.17 to 1.11). Interventions with a longer treatment duration (> 6 weeks) led to more consistent effects on depression.

Conclusions

Guided ICBT appears to be a promising and effective treatment for chronic somatic conditions to improve psychological and physical functioning and reduce disease-related impact. The most consistent improvements were found for disease-specific outcomes, which supports the possible relevance of tailoring interventions to specific patient groups. Explorative analyses revealed that longer treatment length holds the promise of larger treatment effects for the specific outcome of depression. While the current meta-analysis focused on several chronic somatic conditions, future meta-analyses for separate chronic somatic conditions can further consolidate these results, also in terms of cost-effectiveness.

Introduction

Cognitive behavioural therapy (CBT) focuses on challenging cognitive distortions and dysfunctional underlying beliefs, and on teaching coping and problem solving skills [1]. A variety of techniques are combined to achieve this, including cognitive restructuring, relaxation, problem solving, and stress management. The central idea of CBT is that the way people make sense of their environment affects their feelings and behaviour. CBT is an extensively researched and widely used form of treatment for a variety of psychological conditions [1] and is increasingly used to help a growing number of patients suffering from chronic somatic conditions cope with the consequences of their condition [1–5]. CBT models can, for instance, be applied to improve patients' adjustment to receiving a diagnosis of a chronic somatic condition and coping with it, to improve comorbid mood problems such as anxiety and depression, to alter disease-specific beliefs and attitudes, and to teach pain/symptom management strategies [6, 7].

Although studies indicate that CBT may be an effective treatment for chronic somatic conditions, it has not been implemented on a large scale, partly due to the lack of CBT therapists specializing in patients with chronic somatic conditions. Furthermore, chronically ill patients may have physical limitations that make it difficult to travel to a clinic for face-to-face CBT. A possible solution is to offer CBT online: Internet-based cognitive behavioural therapy (ICBT). Generally, ICBT takes the form of an online self-help program, guided by a therapist who gives feedback and answers questions [8]. Advantages of ICBT over offline computerized CBT and over bibliotherapy include the possibility of the patient connecting with a therapist or with peers who cope with similar problems, and the ability to log on and use the intervention anytime and anywhere they would like. ICBT may be beneficial to both patients and therapists: it is more convenient, flexible, and reduces traveling time, costs, and waiting lists, enabling more patients to be reached and treated [9]. In addition, providing

CBT online may reduce the stigma of needing psychological help. Recently, first indications have been reported for the cost-effectiveness of ICBT [10–12].

Internet interventions are generally found to be effective for a variety of psychological conditions [13–16]. Preliminary evidence is also emerging for its effect on psychological and physical outcomes in various health problems [17–21] and in promoting health behaviour change [22, 23]. In order to determine whether ICBT is effective for chronic somatic conditions, the results of the increasing number of recent randomized controlled trials (RCTs) need to be systematically evaluated and quantitatively analyzed. Moreover, knowledge of which types of outcomes are specifically improved by ICBT will provide insight into the types of problems that could be targeted with ICBT.

An additional focus on which elements of interventions are effective for which patients at what disease stage will aid development of effective tailored interventions. Scarce evidence suggests that the amount of therapist contact is related to effectiveness [16]. An aspect of ICBT that has not been examined is whether the duration of ICBT influences treatment outcomes. For traditional face-to-face CBT for chronic somatic conditions, an average treatment of 12–16 sessions given once a week is suggested [24]. Although there are indications in patients with depressive symptoms that a longer ICBT treatment duration yields better outcomes [25], the role of treatment duration has not yet been examined for chronic somatic conditions.

The current review aims to describe and evaluate the effectiveness of guided ICBT interventions in randomized controlled trials, for three specific outcome categories −general psychological outcomes, disease-related physical outcomes, and disease-related impact outcomes− and to explore the role of treatment duration. The review focused on guided

ICBT interventions, in order to optimize comparability with face-to-face CBT and decrease heterogeneity, as it is known that guided ICBT interventions generally lead to different (larger) effects than non-guided self-help interventions [16]. This review has a broad focus, including a large population of chronic somatic conditions. Because the literature on ICBT in different chronic somatic conditions is rather limited at this time, it is not yet possible to meaningfully summarize the evidence for efficacy of ICBT for these separate categories of chronic somatic conditions. Because the main elements of CBT are generic in scope and can be applied to a large variety of problems, combining these different chronic somatic conditions in this meta-analysis provides a first overall indication of the efficacy of ICBT interventions in the large population of chronic somatic conditions. In addition, the separate outcomes for different somatic conditions can also be deduced from the paper.

Methods

Search strategy and inclusion criteria

PubMed, PsycINFO, and Embase were searched from inception until February 2012, by combining index terms indicative of effect studies, internet, and cognitive behaviour therapy, and including the following Medical Subject Heading (MeSH) terms: internet, electronic mail, behaviour therapy, psychotherapy, rehabilitation, counseling, and self-care (see Multimedia Appendix 1 for search strategies). Only studies investigating guided ICBT, which is comparable to face-to-face CBT, were included. All retrieved references were loaded into Endnote, and two raters (SvB, MSc Psychology, HvM, PhD Psychology) independently screened titles and abstracts without blinding to authorship or journal. The full text of potentially relevant studies was examined. Discrepancies between reviewers were resolved by discussion. The kappa statistic was calculated to determine consistency among raters. Inclusion criteria were (1) RCT or equivalence trial, (2) therapy provided with the internet

(not face-to-face, telephone, onsite computerized therapy, videoconferencing, or personal digital assistants) as the main way of communication (e.g., patient spends > 50% of total intervention time spent on an Internet-based intervention), (3) therapy based on CBT principles (in which at least some forms of cognitive and behavioural techniques are used), (4) therapy guided by contact with a therapist, with at least one episode of personalized patient contact (either through asynchronous messages, telephone, or another mode of contact), and (5) adult study sample (age ≥ 18 years) with an existing chronic somatic condition (i.e. a condition expected to last a year or longer, limit what a patient can do, and/or may require ongoing medical care) [26]. Aetiology was not an inclusion criterion; both functional and structural disorders were included. Conditions that may have physical consequences but do not have physical illness as its primary feature, such as eating disorders, insomnia, addiction problems, fertility problems, and sexual dysfunction, were also excluded. Papers not published in English were also excluded. Studies were excluded when the main focus of the intervention was focused on lifestyle change, such as increasing levels of exercise or improving diet. Publications of the same intervention were included if each study was based on a new patient sample. Papers were excluded based on a hierarchical approach, in which articles were not further assessed for remaining reasons if they were excluded based on a previous reason. The hierarchy of reasons for exclusion were that (1) the study does not examine ICBT for chronic somatic conditions, (2) the study is not an RCT, (3) the ICBT intervention is not guided by a therapist, and (4) the study does not examine adult patient populations (see Figure 1).

Data extraction

The following information was gathered per study: publication year, chronic somatic condition, country of data collection, number of patients included, completers, dropouts, dropout reasons, age, gender, type of CBT intervention, therapist contact, control condition,

outcome measures, intervention length, completer or intent-to-treat analyses, post-treatment results, and follow-up results. A large variety of outcome measures were reported across studies. To enable general conclusions, these were grouped together into three main outcome categories that are of relevance to patients with chronic somatic conditions: (1) general psychological outcomes of depression, anxiety, and distress, (2) disease-related physical outcomes related to symptom severity, such as pain, fatigue, and headache, and (3) disease-related outcomes concerning the impact of a chronic somatic condition on daily life (i.e. disease-specific distress and disease-specific quality of life) (see Multimedia Appendix 2). To improve homogeneity and narrow the scope of the review, outcome measures that did not fit these categories (e.g., coping or behaviour) or that were not suitable for pooling in meta-analysis (i.e. because of being assessed infrequently (e.g., general quality of life) or by means of different measures (e.g., disability) were excluded. When more than one outcome was used to measure the same construct, results for the outcome that was most generic (e.g., total scale score versus subscale scores), most validated (e.g., Beck Depression Inventory (BDI [27]) versus Modified Beck Depression Inventory (mBDI [28]), or most comparable to other studies (e.g., visual analogue scale [VAS] of distress versus therapist-rated distress) was used, to prevent separate studies having too much influence on the analysis.

Assessment of risk of bias in included studies

Two independent authors (SvB, MSc Psychology; MF, MSc Psychology) assessed each study using the Cochrane risk of bias tool, including selection bias (randomization process), performance bias (blinding of subjects and personnel), detection bias (blinding of outcome assessment), reporting bias (handling of missing data), and attrition bias (reasons for withdrawal in all conditions) [29]. A third rater (MR, professor of evidence-based surgery) was consulted to reach consensus when two raters were in disagreement. Risk of bias was

assessed based on the information of original publications and on trial registrations on the ClinicalTrials website.

Reporting study results

Only between-group results were taken into account to examine the effect of ICBT as compared to a passive control condition. Passive control conditions were defined as conditions in which participants do not receive a therapeutic program and instead are placed on a waiting list, or receive only treatment as usual or treatment that is theorized to not lead to changes in therapeutic outcomes (e.g., patient education) (see Multimedia Appendix 2). For equivalence trials, in which patients receive an intervention that is theorized to lead to clinically relevant changes in outcomes as an active comparison condition, and for studies with a three-arm design, both between-group effects and main effects are reported (see Multimedia Appendices 3 and 4). Intent-to-treat analyses (ITT), in which all randomized patients are analyzed regardless of adherence to study protocol [30], were used wherever possible. When two active ICBT interventions were compared to a passive control condition in a three-arm RCT design, both comparisons are reported. Two types of dropout rates were calculated: (1) intervention dropouts by dividing the number of patients reported to have stopped the intervention (or did not return post-intervention questionnaires) by the number randomized to the intervention group, and (2) measurement dropouts by dividing the number of patients from both the intervention and control groups who did not return post-intervention questionnaires by the total number of patients randomized. As between-group follow-up results were not consistently and uniformly reported across studies, pooling was not feasible. Therefore, only post-intervention study results are reported and the number of studies that included follow-up results is briefly summarized.

Data analyses and synthesis

Standardized mean difference of effect sizes (SMDs) were calculated by subtracting the difference in means in the ICBT group from the difference in means in the control group and dividing the outcome by their pooled standard deviation [31]. Effect sizes of 0.2, 0.5, and 0.8 can be considered as small, moderate, and large, respectively [32]. When a study contained multiple eligible ICBT treatment groups, these were combined in a single pairwise comparison, according to recommendations and calculation methods from the Cochrane handbook [29]. If mean values and SDs were not reported, authors were contacted to obtain original trial data. When not provided, alternative methods were used (i.e. using reported mean change scores and associated SDs). To decide whether meta-analytic pooling of data was justified, we computed I^2, which describes the percentage of total variation between studies due to heterogeneity rather than chance [33]. An I^2 of 25%, 50%, and 75% can tentatively be considered as low, moderate, and high heterogeneity, respectively [33]. High heterogeneity indicates that the effects are not the same for all studies and that there may be other variables that explain this heterogeneity. As significant heterogeneity is to be expected, SMDs were calculated in random effects models, using Cochrane Collaboration software Review Manager, version 5.1. These models assume that there is no one 'true effect size', but rather the effect sizes are sampled from a population of varying effect sizes [34]. Subgroup differences in intervention duration were analyzed using the chi-square test, with $p < .05$ indicating statistically significant differences.

Results

Search results and study characteristics

The literature search identified 4848 unique studies, 23 of which met the inclusion criteria (see Figure 1) [35–57]. Interrater reliability of study selection was kappa = .805. The included

studies involved 4340 subjects (2299 ICBT and 2041 control); 59% of subjects participated in three large studies by Lorig and colleagues [52–54].

In 74% (17/23) of studies, subjects were randomized to one of two conditions, 15 of which compared ICBT with a passive control condition: waiting-list (12 studies), care-as-usual (2 studies), and information-based psycho-education (1 study) (Multimedia Appendix 2). Three studies compared ICBT with an active CBT control condition: face-to-face group therapy, online stress management without CBT, and ICBT with added telephone contact (Multimedia Appendix 3). Five studies used a three-arm design, two of which reported results of the two joint intervention groups compared to a passive control condition (Multimedia Appendix 2), and three compared each of the three conditions (Multimedia Appendix 4).

A total of 70% (16/23) of studies were published between 2008 and 2011, and 52% (12/23) were carried out in Sweden. Eleven studies (48%) used intent-to-treat (ITT) analyses. The majority of these studies (6/11) used the last observation carried forward (LOCF) method, in which a participant's missing values after dropout are replaced with the last available measurement [58]. Four of the 11 studies used mixed models approaches [59], and one used multiple imputation by chained equations [60]. 74% (17/23) included some form of follow-up assessment ranging from 1-18 months: 10 (43%) used a between-group follow-up and 7 (30%) included a within-group or completers-only follow-up, ranging from 2 months to 1 year. Dropout rates differed widely but were overall relatively high (median 18%, range 2-57%), particularly in the intervention groups (median 29%, range 1-72%) (Multimedia Appendix 2). Of the 5 studies that reported reasons for dropout, the most common reason mentioned was lack of time.

Patient populations

Patient populations included chronic pain (5/23 studies, 21%), headache or migraine (4/23 studies, 17%), tinnitus (4/23 studies, 17%), irritable bowel syndrome (IBS, 4/23 studies, 17%), diabetes (2/23 studies, 8%), breast cancer (1/23 studies, 4%), epilepsy (1/23 studies, 4%), fatigue in patients with chronic neurological disorders (1/23 studies, 4%), and a heterogeneous patient population (1/23 studies, 4%) (Multimedia Appendix 2). Twenty studies of 23 (87%) involved community-based samples. The mean age range of subjects within studies varied between 34 and 66 years; most studies included more female than male subjects.

Intervention content and duration

Interventions consisted of a variety of generic CBT-based techniques, often supplemented with specific approaches appropriate for the chronic condition under study. Interventions focusing on relaxation and psycho-education were included only when combined with other CBT techniques, that is, some form of cognitive reappraisal or restructuring [61]. Treatment content was categorized into well-known CBT elements such as cognitive therapy, behavioural therapy, applied relaxation, and psycho-education (see Multimedia Appendix 2). The vast majority of studies described the interventions as self-help programs with structured modules, which were typically completed in a rate of one module per week, with minimal therapist guidance. The most commonly mentioned intervention components were cognitive therapy techniques, (applied) relaxation, psycho-education, and improving coping skills. These components were mentioned in 74-100% of interventions. Stress management and behavioural therapy techniques were also mentioned in over half of included interventions. Other therapy components, incorporated in 26-35% of interventions, were problem solving techniques, mindfulness-based techniques, exposure, and physical exercise. The majority of interventions were labelled as CBT and/or self-management interventions,

while some interventions were based on acceptance and commitment therapy (ACT) [46], exposure-based treatment in combination with mindfulness techniques [49–51], or mindfulness-based cognitive therapy (MBCT) [56].

Interventions were generally broad and multifaceted, targeting various aspects of chronic somatic conditions within one intervention (e.g., comorbid mental health problems, coping with the chronic somatic condition, and reducing physical symptoms). Incidentally, studies indicated that there was a specific primary aim, for example, to reduce depressive symptoms [56–57], distress associated with the condition [35, 37], or severity of the chronic somatic condition [41, 43, 50]. However, also in the interventions with a more specific aim, components were generally included to fit other aims as well. Therefore, it was not possible to meaningfully categorize interventions according to the intervention aim (e.g., physical, mental, prevention). When analysing the results, the SMDs in each meta-analysis generally did not meaningfully differ from one another, indicating that there are no differences in SMDs according to intervention aim.

Therapist contact and peer contact

All studies incorporated treatment-related contact options, usually in the form of (weekly) email contact with (psychology master students supervised by) licensed clinical psychologists. One study was based solely on therapist-patient contact via email without additional treatment components. Most studies did not report, or not in detail, the average time therapists spent on patients. The main mode of therapist contact was through asynchronous (email) messages, but in three of 23 studies (13%) telephone was the main contact option. Five studies (22%) used online group formats. A total of 43% (10/23) of studies included a bulletin board that enabled patients to interact with each other, as an addition to individual treatment tools.

Risk of bias in included studies

The authors' judgments about risk of bias for each included study and presented as percentages across all included studies can be found in Figures 2 and 3. While the majority of studies (14/23, 61%) reported adequate methods of randomization, 35% (8/23) of studies did not report randomization methods, and 4% (1/23) reported inadequate methods. The study with inadequate methods (e.g., randomization based on order of enrolment [47]) was excluded from primary analyses, as a randomized design was one of the inclusion criteria for this study. To be complete, we also report the results including this study, in a secondary analysis. In eight studies of the 23 (35%), allocation of participants was adequately concealed, while allocation concealment remained unclear in ten of 23 studies (43%) and was at risk for inadequate concealment in 22% (5/23); for example, tossing a coin, picking a piece of paper, or throwing dice. None of the included studies reported blinding of participants, personnel, and outcome assessments, which led to an unclear risk of bias in 43% of studies (10/23; no information on blinding) or a high risk of bias in 57% of studies (13/23; information indicating that blinding did not take place). Over half of all studies had incomplete outcome data that led to a high risk of bias, which was mainly due to a lack of intent-to-treat analyses in 48% (11/23) of studies. The risk of selective reporting bias remained largely unclear, mainly because only 26% (6/23) were registered with the ClinicalTrials site and registration often took place after study completion.

Effectiveness of ICBT interventions

SMDs for the included outcomes are reported in Multimedia Appendix 2 for the 17 studies with a passive control condition, Multimedia Appendix 3 for the 3 studies with an active control condition, and Multimedia Appendix 4 for the 3 studies with a three-arm design. Pooled SMDs for the three outcome categories can be found in Table 1.

General psychological outcomes

Sixteen of 17 studies comparing ICBT with a passive control condition included general psychological outcomes, 5 of which (31%) found greater improvements in the ICBT condition on at least one outcome (see Multimedia Appendices 2 and 4). ICBT had similar effects as active treatment control conditions (see Multimedia Appendices 3 and 4). Pooled SMDs for depressive symptoms, anxious symptoms, and general distress yielded small but generally statistically significant effects (see Table 1 and Figures 4 to 6). For depressive symptoms, results of a sensitivity analysis excluding one outlier with a very large effect on depression [SMD 4.34; 56] are reported; if included, the SMD would be 0.32 (k = 16, 95% CI 0.09 -0.55, p = .005, I^2 = 78%).

Disease-related physical outcomes

Seventeen studies comparing ICBT with a passive control condition included disease-related physical outcomes, with 59% (10/17) finding effects in favor of the ICBT condition on at least one outcome (see Multimedia Appendices 2 and 4). Pooled SMDs for physical outcomes yielded varying results. Large effects were found for IBS symptoms, moderate effects for headache, small effects for pain and fatigue, and non-significant effects were found for tinnitus loudness, sleep quality, and glycaemic control (see Table 1). In the case of IBS symptoms, one study was excluded based on inadequate randomization procedures. A secondary sensitivity analysis including this study led to very similar results as the primary analysis (pooled SMD 1.14, 95% CI 0.81-1.48, p < .001, I^2 = 0%, k =3). Studies with an active control condition were not pooled due to a limited number of studies and comparable outcomes (see Multimedia Appendices 3 and 4 for the results of individual studies).

Disease-related impact on daily life

Nine studies with a passive control condition included measures of disease-related distress or quality of life, of which seven (78%) found effects in favor of the ICBT condition on at least

one outcome (see Multimedia Appendices 2 and 4). Small but significant effects were found on disease-related distress, and large effects were found on disease-specific quality of life (see Table 1 and Figures 7 and 8). In the case of disease-specific quality of life, one study was excluded based on inadequate randomization procedures. A secondary sensitivity analysis including this study led to very similar results as the primary analysis (pooled SMD 1.09, 95% CI 0.80-1.39, $p < .001$, $I^2 = 0\%$, $k = 4$). Results from studies with an active control condition were not pooled due to a limited number of studies and outcomes. Individual study results can be found in Multimedia Appendices 3 and 4.

Role of treatment duration in intervention effectiveness

Most interventions were relatively short, with little variability in treatment duration: 4% (1/23) of the interventions lasted 4 weeks, 48% (11/23) lasted 6 weeks, and 48% (11/23) lasted 7-24 weeks (see Multimedia Appendix 2). Consequently, outcomes of the studies in which the intervention lasted ≤ 6 weeks and > 6 weeks were compared. Of the 5 studies finding a between-group effect on depression, 4 (80%) had an intervention duration of > 6 weeks. Effect sizes of the longer interventions ($n = 8$; SMD 0.29; 95% CI 0.13-0.46) were larger than those in the shorter interventions, with marginal statistical significance ($n = 7$; SMD 0.08; 95% CI -0.05 to 0.22) ($\chi^2_1=3.91$, $p=.05$). Intervention duration did not influence effectiveness for other outcomes.

Discussion

Principal findings

Our meta-analysis indicates that ICBT is effective for chronic somatic conditions regarding both general psychological outcomes and disease-specific outcomes. Effect sizes were generally small to moderate, with larger effect sizes occasionally found for disease-related outcomes, such as self-reported headache and IBS symptoms, and for disease-specific quality of life. These findings of larger effects on disease-specific outcomes may on the one hand reflect the larger sensitivity to change of these measures [62, 63] and on the other hand support the idea of tailoring interventions to the needs of specific patient groups, as disease-specific measures are likely the measures that respond well to more tailored, disease-specific approaches [64–67].

The three included studies that compared ICBT with an active treatment condition showed that ICBT can be as effective as group-based face-to-face CBT, for example. However, two studies also found that ICBT and an informational website without CBT content were similarly effective. These results indicate a need for studies in which the effects of specific components of ICBT are more closely investigated. The role of one such component of ICBT was examined in this meta-analysis −intervention length− suggesting that interventions lasting longer than 6 weeks result in greater improvements in depression.

Overall, results of this review extend previous reviews and meta-analyses, which concluded that ICBT may be a promising adjuvant treatment for psychological outcomes [13–16] and for patients with health problems [17–23]. Meta-analyses have typically reported small [18] to moderate [14, 16] pooled effect sizes for Internet-based psychotherapeutic interventions. The results are also comparable to meta-analyses of face-to-face CBT, which typically find

small to moderate effect sizes on a variety of outcomes [1, 68–70], with sometimes larger disease-specific than more general mood-related effects [69]. Our review adds to previous findings by including all available studies in chronic somatic populations and by identifying differences in effectiveness for specific categories of outcome. With this approach, it was shown for the first time that guided ICBT is effective for various psychological and physical outcomes, with most promising results for disease-related outcomes, and that intervention duration might be a determinant of the effectiveness of ICBT for depression. These results underline the potential benefit of ICBT for patients with chronic somatic conditions in helping them cope with the consequences of their condition.

Limitations

Some potential limitations should be discussed. First, there are still a limited number of studies on ICBT in chronic somatic conditions, and sometimes only one study was available for a specific condition, which precludes drawing reliable conclusions about specific patient groups and generalizing across conditions. Over half of the studies were performed in Sweden by the same authors, but post-hoc analyses did not find differences in outcomes between the Swedish and other studies (data not shown). Women constituted a large proportion of most study populations, reflecting the often unequal gender distribution of different chronic somatic conditions. Second, studies were found to be of variable methodological quality, which may influence both individual study results and overall outcomes in meta-analysis. Although all studies had unclear or high risk of blinding bias, this is often unfeasible or very difficult to achieve in non-pharmacological behavioural interventions and thus may not be a valid indicator of study quality [71]. In many studies, inadequate descriptions resulted in unclear risk of bias. This may be resolved by using guidelines for reporting RCTs [72]. Third, the appropriateness of pooling studies of ICBT for various patient populations can be discussed, as pooling is intended for more or less

homogeneous populations and outcomes. The current review included a relatively diverse range of chronic somatic conditions, and outcomes were often assessed with various different questionnaires. However, similar effects and low heterogeneity were found for most outcomes, supporting the idea that the included studies were comparable regarding their outcomes. Including these various studies in this meta-analytic overview provides the reader with a first indication of the overall effectiveness of ICBT for chronic somatic conditions and increases the generalizability of findings [73, 74]. As more trials become available in the future, meta-analyses should be performed for separate chronic somatic conditions. Fourth, long-term between-group follow-up measurements were often lacking, precluding a reliable long-term estimate. Fifth, there was substantial variation in description of treatment content, therapist contact, and dropout. For instance, not all therapist contact was with a trained therapist but could also include "expert" patients, nurses, physicians, occupational therapists, or research assistants. Dropout rates were not always adequately described and generally high, which is a common problem with internet interventions [75]. Sixth, publication bias cannot be precluded. The current review was limited to published studies, as it was unfeasible to obtain a complete and unbiased overview of all unpublished grey literature on this subject. This may have led to an overestimation of effectiveness, as published studies are generally more likely to include statistically significant results [76]. However, several studies that did not find an effect were included in the current review, indicating that not only studies with significant results are published on this topic.

Finally, we used the pooled standard deviation based on pre- and post-intervention measurements in our meta-analysis. When using change scores in meta-analysis, the most appropriate measure would have been the standard deviation of changes. However, the included studies did not report sufficient information to calculate these standard deviations [29], which has been recognised as a common problem when using change scores. Our

approach can, however, be considered as a conservative approach since the calculated standard deviations will be slightly larger than the standard deviations of changes would have been. Another alternative would have been to perform the meta-analysis based on post-intervention measurements, but such an approach does not take into account possible differences in baseline measurements. Nevertheless, we also performed a meta-analysis based on post-intervention measurements results. The results of this meta-analysis were very similar to the change score results reported in our study (data not shown), and would have led to similar conclusions.

Future research

Results from this review suggest several areas for future research, related to study methodology and intervention design. More studies with adequate sample sizes focusing on a wider range of chronic somatic conditions with between-group long-term follow-up are needed. Only one study involved older patients [38], yet older patients are often affected by chronic conditions. As dropout is common with ICBT, ways to promote engagement and improve adherence should be investigated. Preliminary research suggests that tailoring interventions may be an effective strategy to promote engagement and adherence [77–79]. Strategies found to be predictive for adherence include increased therapist contact, more frequent website updates, and more frequent intended usage [80]. Also, future research is needed to examine the effects of ICBT on outcomes such as work-related outcomes, health behaviours, and cost-effectiveness, which were not evaluated in this meta-analysis in order to narrow its scope. Last, the "active ingredients" of interventions need to be identified, in order to develop effective interventions for specific problems. Additional control conditions including "sham" treatment websites should be included to assess the specific value of ICBT [81]. Analyses on computer-generated data about how subjects access the website may also be a worthwhile approach to examine engagement, usability, and active ingredients [82].

Conclusions

The current review indicates that ICBT interventions improve both psychological and disease-related physical outcomes in patients with chronic somatic conditions, with small-to-medium effect sizes. Larger improvements are occasionally found for disease-specific outcomes related to daily-life impact of the illness, which underlines the importance of tailoring interventions to specific (patient) groups. Our results also indicate that interventions of longer duration may be more effective for psychological outcomes such as depression, which implies that tailoring the duration of interventions to specific problems may be appropriate.

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Multimedia Appendix 1

Search strategies

Pubmed search strategy

("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR random*[tiab] OR non-inferiority[tiab] OR equivalen*[tiab] OR rct[tiab] OR single blind[tiab] OR double blind[tiab] OR t r iple blind[tiab]) AND ("Internet"[Mesh] OR internet*[tiab] OR web*[tiab] OR online[tiab] OR "Therapy, Computer-Assisted"[Mesh] OR ehealth[tiab] OR e-health[tiab] OR "electronic mail"[MeSH Terms] OR "electronic mail"[tiab] OR "e mail"[tiab] OR email[tiab] OR cyber*[tiab] OR icbt[tiab] OR i-cbt[tiab] OR wcbt[tiab] OR w-cbt[tiab]) AND ("Behavior Therapy"[Mesh] OR psychotherapy[mesh] OR "rehabilitation"[Subheading] OR "rehabilitation"[tiab] OR "rehabilitation"[MeSH Terms] OR psychoeducational[tiab] OR psychoeducation[tiab] OR psycho-educational[tiab] OR psycho-education[tiab] OR "Counseling"[Mesh] OR counselling[tiab] OR counseling[tiab] OR ((therapy[tiab] OR therapies[tiab] OR treatment*[tiab]) AND (cognitive[tiab] OR behavior[tiab] OR behavioural[tiab] OR behaviour[tiab] OR behavioural[tiab] OR conditioning[tiab] OR cognition[tiab])) OR "Behavior Therapy"[Mesh] OR behavior modification[tiab] OR behaviour modification[tiab] OR conditioning therapy[tiab] OR conditioning therapies[tiab] OR conditioning treatment[tiab] OR cognition therapy[tiab] OR cognition therapies[tiab] OR cognitive psychotherapy[tiab] OR cognitive psychotherapies[tiab] OR cognitive t reatment[tiab] OR "Self Care"[Mesh] OR self care[tiab] OR self help[tiab] OR self management[tiab])

PsycINFO search strategy

((internet* or web* or online* or computer* or electronic* telemedicine or websites or ehealth or e-health or e-mail or email or electronic mail or cyber* or icbt or i-cbt or wcbt). ti,ab. or

(internet or online therapy or telemedicine or computer assisted therapy or computer mediated communication).sh.) AND ((random* or non-inferiority or equivalen* or rct or single blind or double blind or triple blind).ti,ab. OR (("quantitative study" or "empirical study" or follow up study or "treatment outcome/clinical trial").md. AND random*.af) OR exp evidence based practice/ or clinical trials/ or treatment effectiveness evaluation/) AND (exp cognitive behavior therapy/ or exp behavior modification/ or exp behavior therapy/ or exp cognitive restructuring/ or exp cognitive therapy/ or exp dialectical behavior therapy/ or (rehabilitation or psychoeducational or psychoeducation or psycho-educational or psycho-education or counselling or counseling or ((therapy or therapies or treatment*) and (cognitive or behavior or behavioural or behaviour or behavioural or conditioning or cognition)) or behavior modification or behaviour modification or conditioning therapy or conditioning therapies or conditioning treatment or cognition therapy or cognition therapies or cognitive psychotherapy or cognitive psychotherapies or cognitive treatment or self care or self help or self management).ti,ab. or self management/ or exp cognitive therapy/ or exp self monitoring/)

Embase search strategy

((internet* or web* or online* or computer* or electronic* telemedicine or websites or ehealth or e-health or e-mail or email or electronic mail or cyber* or icbt or i-cbt or wcbt). ti,ab. or (internet or exp telehealth/ or computer assisted therapy or computer assisted therapy).sh.) AND ((random* or non-inferiority or equivalen* or rct or single blind or double blind or t r iple blind).ti,ab. or (randomized controlled trial or evidence based practice).sh. or (therapy effect.sh. and random*.af.)) AND (exp cognitive therapy/ or exp behavior modification/ or exp behavior therapy/ or exp self care/ or exp self monitoring/ or (rehabilitation or psychoeducational or psychoeducation or psychoeducational or psycho-education or counselling or counseling or ((therapy or therapies or treatment*) and (cognitive or behavior

or behavioural or behaviour or behavioural or conditioning or cognition)) or behavior modification or behaviour modification or conditioning therapy or conditioning therapies or conditioning treatment or cognition therapy or cognition therapies or cognitive psychotherapy or cognitive psychotherapies or cognitive treatment or self care or self help or self management).ti,ab.)

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition

Table 1. Pooled SMDs for ICBT versus passive control conditions

Outcome category	*k*[a]	SMD[b]	95% CI	*z*	*p*	I^2 (%)
General psychological outcomes						
Depressive symptoms	15	0.21	0.08-0.34	3.18	.001	29
Anxious symptoms	10	0.17	0.01-0.32	2.14	.03	0
General distress	6	0.21	0.00-0.41	1.98	.05	0
Disease-related physical outcomes						
IBS symptoms	2	1.19	0.82-1.57	6.25	<.001	0
Headache	3	0.49	0.21-0.77	3.41	<.001	0
Sleep quality	3	0.25	-0.02 to 0.53	1.80	.07	0
Pain	6	0.18	0.08-0.28	3.61	<.001	0
Fatigue	2	0.15	0.05-0.26	2.87	<.01	0
Tinnitus loudness	2	-0.04	-0.40 to 0.32	0.24	.81	0

Glycemic control	2	0.07	-0.17 to 0.30	0.54	.59	62
Disease-related impact outcomes						
Disease-specific quality of life	3	1.11	0.79-1.44	6.73	<.001	0
Disease-specific distress	6	0.17	0.03-0.31	2.41	.02	57

Note. IBS = irritable bowel syndrome.

[a]*k* = number of comparisons, [b] SMD =standardized mean difference.

Multimedia appendix 3. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with an active comparison condition

Author, year (population)	**Condition, *N***	**Dropout *n* (%)**	**Treatment content (duration)**	**Outcome**	**Outcome measure[a]**	**Between group effects[b]**
Abbott et al, 2009 [35] (tinnitus)	ICBT, 32	Intervention 23/32 (72%)	**ICBT (6 wks)** -applied relaxation -cognitive therapy -behavioural therapy -psychoeducation -improving coping skills	**General psychological**		ITT
				depression	DASS-D	0
				anxiety	DASS-A	0
	Online psychoeducation, 24	Measurement 32/56 (57%)		stress	DASS-S	0
				Disease-related physical		
				tinnitus loudness	VAS	0
				quality of sleep	VAS	0
				Disease-related impact		
				tinnitus-related distress and annoyance	TRQ	0

Andersson et al, 2002 [37] (tinnitus)	ICBT, 53	Intervention 26/53 (49%)	**ICBT (6 wks)** -applied relaxation -cognitive therapy -behavioural therapy -mindfulness & acceptance-based techniques -psychoeducation -improving coping skills	**General psychological**		Non-ITT
				depression	HADS-D	– [e]
				anxiety	HADS-A	– [e]
				Disease-related physical		
	Waiting list, 64	Measurement 45/117 (38%)		tinnitus loudness	VAS	– [d]
				quality of sleep	VAS	0 [c]
				Disease-related impact		
				tinnitus-related distress and annoyance	TRQ	– [e]

Multimedia appendix 4. Study characteristics and between-group post-intervention effects of ICBT for chronic somatic conditions: three-armed studies with two active treatment conditions and one passive control condition

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
van Bastelaar et al, 2011 [57] (type 1 and 2 diabetes)	ICBT, 125	Intervention 72/125 (58%)	**ICBT (8 wks)** -cognitive therapy -applied relaxation -behavioural therapy -stress management -improving coping skills	**General psychological**		ITT
				depression	CES-D	– [f]
				Disease-related physical		
	Waiting list, 130	Measurement 88/255 (35%)		glycemic control	HbA1c	*n.r.*
				Disease-related impact		
				diabetes-specific emotional distress	PAID	– [f]
Berman et al, 2009 [38] (chronic pain)	ICBT, 52	Intervention 10/52 (19%)	**ICBT (6 wks)** -applied relaxation -cognitive therapy (group) -psychoeducation	**General psychological**		Non-ITT
	Waiting list, 37	Measurement 11/89 (12%)		depression	CES-D	0
				anxiety	STAI-6	0
				Disease-related physical		
				pain intensity	BPI	0
				Disease-related impact		
				–	–	–

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Burhman et al, 2011 [41] (chronic back pain)	ICBT, 26	Intervention 3/26 (12%)	**ICBT (8 wks)** -applied relaxation -cognitive therapy -stress management -improving coping skills -mindfulness -physical exercise -psychoeducation	**General psychological**		ITT
				depression	HADS-D	0
				anxiety	HADS-A	0
				affective distress	MPI	0
	Waiting list, 28	Measurement 4/54 (7%)		**Disease-related physical**		
				pain severity	MPI	0
				Disease-related impact		
				–	–	–
David et al, 2011 [42] (breast cancer)	ICBT, 69	Intervention 37/69 (54%)	**ICBT (8 wks)** -psychoeducation -cognitive therapy -behavioural therapy -stress management -improving coping skills -problem solving	**General psychological**		Non-ITT
				depression	BSI	0
				anxiety	BSI	0
				psychological distress	BSI-GSI	0
	Waiting list, 64	Measurement 63/133 (47%)		**Disease-related physical**		
				–	–	–
				Disease–related impact		
				–	–	–

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Devineni and Blanchard, 2005 [43] (chronic headache)	ICBT, 39[g]	Intervention *n.r.*	**ICBT (4 wks)** -applied relaxation -cognitive therapy -stress management -improving coping skills -biofeedback	**General psychological**		Non-ITT
	Waiting list, 47[g]	Measurement 53/139 (38%)		depression	CES-D	0
				anxiety	STAI-T	0
				Disease-related physical		
				headache index	Diary	–[f]
				Disease-related impact		
				–	–	–
Hunt et al, 2009 [47] (irritable bowel syndrome)	ICBT, 28	Intervention 15/28 (54%)	**ICBT (6 wks)** -applied relaxation -stress management -improving coping skills -cognitive therapy -behavioural therapy -exposure -psychoeducation	**General psychological**		Non-ITT
				–	–	–
				Disease-related physical		
	Waiting list (+self-monitoring), 26	Measurement 23/54 (43%)		gastrointestinal symptom severity	GSRS	–[e]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+[d]

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Ljótsson et al, 2010 [50] (irritable bowel syndrome)	ICBT, 43	Intervention 13/43 (30%)	**ICBT (10 wks)** -exposure -mindfulness & acceptance-based techniques -cognitive therapy -behavioural therapy -psychoeducation	**General psychological**		ITT
				depression	MADRS-S	0 [h]
				Disease-related physical		
	Waiting list + discussion forum, 43	Measurement 5/86 (6%)		IBS symptom severity	GSRS-IBS	– [f]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+ [f]
Ljótsson et al, 2011a [49] (irritable bowel syndrome)	ICBT, 30	Intervention 7/30 (23%)	**ICBT (10 wks)** -exposure -mindfulness & acceptance-based techniques -cognitive therapy -behavioural therapy -psychoeducation	**General psychological**		ITT
				–	–	–
				Disease-related physical		
	Waiting list + discussion forum, 31	Measurement 11/61 (18%)		IBS symptom severity	GSRS-IBS	– [f]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+ [f]

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Lorig et al, 2006 [53] (hetero-geneous)	ICBT, 457	Intervention 104/457 (23%)	**ICBT (6 wks)** -psychoeducation -physical exercise -cognitive therapy -stress management -improving coping skills -relaxation -problem solving	**General psychological**		Non-ITT
	CAU, 501	Measurement 175/958 (18%)		–	–	–
				Disease-related physical		
				pain	VNS	– [e]
				fatigue	VNS	– [d]
				Disease-related impact		
				health distress	HDS	– [d]
Lorig et al, 2008 [54] (arthritis or fibromyalgia)	ICBT, 433	Intervention 123/433 (28%)	**ICBT (6 wks)** -psychoeducation -physical exercise -cognitive therapy -applied relaxation -stress management -improving coping skills -problem solving	**General psychological**		ITT
	CAU, 422	Measurement 214/855 (25%)		–	–	–
				Disease-related physical		
				pain	VNS	– [f]
				fatigue	VNS	0 [c]
				Disease-related impact		
				health distress	HDS	– [f]
				Outcome	Outcome measure a	Between group effectsb
				General psychological		ITT
				depression	PHQ	0
				Disease-related physical		
				glycemic control	A1c	0c
				Disease-related impact		
				health distress	HDS	0

				General psychological		Non-ITT
				depression	BDI	0
				Disease-related physical		
				headache index	Diary	– d
				Disease-related impact		
				–	–	–
				General psychological		Non-ITT
				depression	BDI	– f
				Disease-related physical		
				–	–	–
				Disease-related impact		
				physical health quality of life	BRFSS	0

Note. [a]BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; BRFSS=Behavioural Risk Factor Surveillance System; BSI=Brief Symptom Inventory; BSI-GSI=Brief Symptom Inventory - Global Severity Index; CAU=Care as usual; CES-D=Centre for Epidemiologic Studies – Depression; DASS-A=Depression Anxiety Distress Scales - Anxiety; DASS-D=Depression Anxiety Distress Scales - Depression; DASS-S=Depression Anxiety Distress Scales - Stress; GSRS=Gastrointestinal Symptom Rating Scale; GSRS-IBS=Gastrointestinal Symptom Rating Scale - Irritable Bowel Syndrome; HADS-A=Hospital Anxiety and Depression Scale - Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; HbA1C=Hemoglobin A1C; HDS=Health Distress Scale; IBS=irritable bowel syndrome; IBS-QOL=Irritable Bowel Syndrome Quality of Life Instrument; ICBT=Internet-based cognitive therapy; ITT=intent-to-treat analysis; MADRS-S=Montgomery-Åsberg Depression Rating Scale self-rating; MPI=Multidimensional Pain Inventory; PAID=Problem Areas in Diabetes; PHQ=Patient Health Questionnaire; SF-36=Short Form Health Survey-36; STAI-S=State

Trait Anxiety Inventory - State Anxiety; STAI-T=State Trait Anxiety Inventory - Trait Anxiety; TRQ=Tinnitus Reaction Questionnaire; VAS=Visual Analogue Scale; VNS=Visual Numeric Scale, [b]0 = no statistically significant effects, – = statistically significant effect indicating a reduction in the outcome, + = statistically significant effect showing an increase in the outcome, [c]$p \leq .1$, [d]$p < .05$, [e]$p \leq .01$, [f]$p \leq .001$, [g]after dropout, pre-dropout sample size not reported, [h]Per-protocol means and SDs are reported in the article (ITT did not affect results, except for non-significance of effect on MADRS-S).

Multimedia appendix 3. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with an active comparison condition

Author, year (population)	**Condition, *N***	**Dropout *n* (%)**	**Treatment content (duration)**	**Outcome**	**Outcome measure[a]**	**Main effects ICBT[b]**	**Between group effects[b]**
Andersson et al, 2003 [36] (recurrent headache)	ICBT + phone, 24	Intervention 7/24 (29%)	**ICBT (6 wks)** -applied relaxation -problem solving -cognitive therapy -psychoeducation -improving coping skills	**General psychological**		Non-ITT	
				depression	HADS-D	– [c]	0
				anxiety	HADS-A	0	0
				self-perceived stress	PSS	– [d]	0
	ICBT - phone, 20	Measurement 20/44 (45%)		**Disease-related physical**			
				headache index	Diary	0	0
				Disease-related impact			
				–	–	–	–
Kaldo et al,	ICBT, 26	Intervention	**ICBT (6 wks)**	**General psychological**		ITT	

2008 [48]		10/26 (38%)	-applied relaxation	depression	HADS-D	– [g]	0
			-cognitive therapy	anxiety	HADS-A	– [h]	0
(tinnitus)	Group-based CBT, 25	Measurement 2/51 (4%)	-behavioural therapy	perceived stress	VAS	0	0
			-exposure	**Disease-related physical**			
			-stress management	tinnitus loudness	VAS	– [h]	0
			-improving coping skills	quality of sleep	ISI	+ [h]	0
			-psychoeducation	**Disease-related impact**			
			-problem solving	tinnitus-related distress and annoyance	TRQ	– [h]	0

Multimedia appendix 3. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with an active comparison condition (continued)

Author, year (population)	**Condition, *N***	**Dropout *n* (%)**	**Treatment content (duration)**	**Outcome**	**Outcome measure[a]**	**Main effects ICBT[b]**	**Between group effects[b]**
Ljótsson et al, 2011b [51] (irritable bowel syndrome)	ICBT, 98	Intervention1 /98 (1%)	**ICBT (10 wks)** -mindfulness & acceptance-based techniques -exposure -behavioural therapy -cognitive therapy	**General psychological**		ITT	
				depression	HADS-D	– [e]	0
				anxiety	HADS-A	– [e]	0
				self-perceived stress	PSS	– [c]	0
	Internet stress	Measurement 4/195 (2%)	**Stress Management (10 wks)** -stress management	**Disease-related physical**			
				IBS symptom severity	GSRS-IBS	– [e]	– [e,f]

	manageme nt (no exposure content), 97		-improving coping skills -problem solving -psychoeducation	**Disease-related impact**			
				disease-specific quality of life	IBS-QOL	+ [e]	– [e,f]

Note. [a]GSRS-IBS=Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; IBS-QOL=Irritable Bowel Syndrome Quality of Life Instrument; ICBT = internet-based cognitive behavioural therapy; ISI=Insomnia Severity Index; ITT=intent-to-treat analysis; PSS=Perceived Stress Scale; TRQ=Tinnitus Reaction Questionnaire; VAS=Visual Analogue Scale, [b]0 =no statistically significant effects, – =statistically significant effect indicating a reduction in the outcome, + =statistically significant effect showing an increase in the outcome, [c]$p < .05$, [d]$p \leq .01$, [e]$p \leq .001$, [f]Favoring ICBT, [g]Only for the Internet condition, [h]p-value not reported.

Multimedia appendix 4. Study characteristics and between-group post-intervention effects of ICBT for chronic somatic conditions: three-armed studies with two active treatment conditions and one passive control condition

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Comparison	Between group effects[b]
Ghahari et al, 2010 [44] (fatigued patients with neurological conditions)	ICBT, 34	Intervention 10/34 (29%)	**ICBT (7 wks)** -stress management -improving coping skills -psychoeducation -cognitive therapy	**General psychological**			ITT
						ICBT - control	0
	Online self-management, 28			depression	DASS-D	Info only - control	0
						ICBT - info only	0
	Care as usual, 33					ICBT - control	0
				anxiety	DASS-A	Info only - control	0
						ICBT - info only	0

		Measurement 10/95 (11%)	**Online self-managemen** **(7 wks)** -stress management -improving coping skills -psychoeducation			ICBT - control	0
				stress	DASS-S	Info only - control	0
						ICBT - info only	0
				Disease-related physical			
				–	–	–	–
				Disease-related impact			
				–	–	–	–

Multimedia appendix 4. Study characteristics and between-group post-intervention effects of ICBT for chronic somatic conditions: three-armed studies with two active treatment conditions and one passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Comparison	Between group effects[b]
Hedborg & Muhr, 2011 [45] (migraine)	ICBT, 28	Intervention 6/55 (11%)	**ICBT (6 months)** -stress management -improving coping skills -applied relaxation -cognitive therapy -physical exercise -behavioural therapy -psychoeducation	**General psychological**			ITT
						ICBT+ - control	0
	ICBT + massage, 27			depression	MADRS-S	ICBT - control	0
						ICBT+ - ICBT	0
	Control, 28			**Disease-related physical**			
		Measurement 7/83 (8%)				ICBT+ - control	– [c]
				migraine frequency	Diary	ICBT - control	– [c]
						ICBT+ - ICBT	0
				Disease-related impact			
				–	–	–	–

Multimedia appendix 4. Study characteristics and between-group post-intervention effects of ICBT for chronic somatic conditions: three-armed studies with two active treatment conditions and one passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Comparison	Between group effects[b]
Hesser et al, 2012 [46] (tinnitus)	ICBT, 32	Intervention 10/67 (15%)	**ICBT (8 wks)** -applied relaxation -cognitive therapy -behavioural therapy -exposure -stress management -improving coping skills -psychoeducation -problem solving	**General psychological**			ITT
						ICBT - control	0
				depression	HADS-D	IACT - control	– [d]
	IACT, 35					ICBT - IACT	0
						ICBT - control	– [d]
				anxiety	HADS-A	IACT - control	– [c]
						ICBT - IACT	0
						ICBT - control	0

	Discussion forum, 32	Measurement 4/99 (4%)	**IACT (8 wks)** -mindfulness & acceptance-based techniques -behavioural therapy -cognitive therapy -psychoeducation	stress	PSS	IACT - control	– [d]
						ICBT - IACT	0
				Disease-related physical			
						ICBT - control	0
				sleep quality	ISI	IACT - control	0
						ICBT - IACT	0
				Disease-related impact			
				–	–	–	–

Note. [a]DASS-A=Depression Anxiety Distress Scales - Anxiety; DASS-D=Depression Anxiety Distress Scales - Depression; DASS-S=Depression Anxiety Distress Scales - Stress; HADS-A=Hospital Anxiety and Depression Scale - Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; IACT=Internet-based acceptance and commitment therapy; ICBT = internet-based cognitive behavioural therapy; ICBT^{+} = ICBT with added hand massage; ISI=Insomnia Severity Index; ITT=intent-to-treat analysis; MADRS-S=Montgomery-Åsberg Depression Rating Scale self-rating; PSS=Perceived Stress Scale, [b]0 =no statistically significant effects, – =statistically significant effect indicating a reduction in the outcome, + =statistically significant effect showing an increase in the outcome, [c]$p < .05$, [d]$p \leq .01$.

CHAPTER 3

What patients think about E-health: Patients' perspective on internet-based cognitive behavioural treatment for patients with rheumatoid arthritis and psoriasis.

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Abstract

Objective

In the past decade, the use of internet-based cognitive behavioural treatments (internet-based CBT) for a wide range of patients has grown intensively. Incorporating the patients' opinions and perspective into new healthcare innovations might improve the quality and applicability of these innovations, as high drop-out rates and low attrition are often-reported concerns in E-health research. Most studies to date have examined patient perspectives on specific internet-based interventions that patients had participated in, and not the views of the general public. The current paper explores the perspective of patients with rheumatoid arthritis and psoriasis on internet-based CBT for these patient groups.

Methods

In total, 100 patients (55% male) participated in a semi-structured telephone interview about internet-based CBT, including questions about possible advantages and disadvantages and the readiness to participate in this kind of treatment.

Results

Most patients (78%) were prepared to participate in internet-based CBT. Patients endorsed the advantages (57%) more often than the disadvantages (34%). The ease of internet-based CBT and the time saved were especially appealing to patients. Main disadvantages according to patients are that not all patients will be reached due to computer illiteracy and the lack of face-to-face interaction with the therapist.

Conclusion

The results suggest that, from the patients' perspective, internet-based CBT is a promising healthcare development. Further research into aspects such as therapist interaction and enhancing computer literacy might contribute to an effective way of E-health care delivery in the future.

Introduction

The patient is increasingly becoming an active participant in the decision making process in clinical practice [1,2]. Especially in non-pharmacological treatments, the patients' effort is essential to the success of the treatment. In recent years, E-health innovations have increasingly become a part of healthcare for a diversity of populations, including for patients with chronic somatic conditions such as rheumatoid arthritis and psoriasis, as they might offer cost-effective ways of delivering healthcare [3].

Up to now, studies into the effectiveness of internet-based cognitive behavioural treatments (internet-based CBT) frequently report high dropout rates and low levels of adherence to the treatment protocol [4-8]. Therefore, incorporating the patient perspective could potentially enhance patient satisfaction, promote adherence, and decrease dropout rates [6-8]. However, only a few studies on the patient perspective have been published, and usually the patient perspective is assessed after patients have taken part in an E-health intervention [9].

Several potential advantages of internet-based CBT have been mentioned [4,10-13], such as the absence of traveling time and costs, as well as freedom of choosing when and where to take part in therapy. Yet there are also some disadvantages to using internet-based interventions [4,10-13]. Often mentioned are issues concerning internet access and proficiency in using computers. For patients with rheumatoid arthritis, disease-specific symptoms such as pain in the upper extremities could lead to discomfort and limit computer use [14].

Despite the potential to improve the use and efficacy of E-health applications, the research of the patient perspective on these applications is limited [15] and often based on evaluations of a specific intervention [9]. The current paper systematically explores the patient perspective of patients with rheumatoid arthritis and psoriasis on internet-based CBT, in order to apply this knowledge to E-health developments.

Patients and methods

Patient characteristics

A convenience sample of fifty patients with rheumatoid arthritis and 51 patients with psoriasis from the out-patient rheumatology and dermatology departments of the Radboud University Nijmegen Medical Centre were asked to participate in a semi-structured telephone interview about healthcare innovations. One patient with psoriasis declined participation due to a lack of interest. Out of the 100 participants, 55 were male patients. The age of the patients ranged from 21 to 83 years, with a mean age of 54.4 years (*SD*=13.4). Patient groups did not differ in age, gender or home internet access (all *P*-values >.05). None of the patients had received internet-based CBT at the time of the interview.

Procedure and measurement instrument

To explore the patient perspective of internet-based CBT, a semi-structured telephone interview was developed for this study, incorporating the possible advantages and disadvantages of internet-based CBT mentioned in the literature (Table 1) [4,5,13,16,17]. Before the interview, patients were given an explanation of internet-based CBT (see Appendix 1). Following, patients were asked whether they endorsed six possible disadvantages of internet-based CBT (yes/no). Then, patients were asked to mention other potential disadvantages that had not been mentioned. The same procedure was followed for

seven possible advantages followed by the same open question. Hereafter participants were asked about how often they would like to be in contact with the therapist and if and how often they would like to meet the therapist face-to-face. Participants were asked to rate on a 10-point scale how important the following aspects were to them: usability and security of the website, accessibility of the therapist, and layout of the website. This was followed by an open-ended question about other aspects patients might find important. Lastly, participants were asked whether they would be willing to participate in internet-based CBT on a 1 to 5 scale (1: 'No, I would rather not'; 2: 'Yes, but I would prefer a face-to-face treatment'; 3: 'Yes, but only if I Have seen the therapist at least once'; 4: 'Yes, I do not have a preference for either a face-to-face treatment or internet-based CBT'; 5: 'Yes, I would prefer treatment by internet-based CBT').

Table 1

The possible disadvantages and advantages of internet-based CBT as described in the semi-structured interview.

Disadvantages	**Advantages**
Not all patients can be reached, e.g. because they do not have a computer with an internet connection.	There is no travel time and no travel costs.
Experience with the computer is required to participate in therapy.	You do not have to wait for the consultation.
You cannot see the therapist (e.g., you cannot see body language and facial expressions).	You will not encounter acquaintances (for example in the waiting room of the therapist).
You have to regularly spend time on the computer.	You decide when you want to take treatment.
You might need more discipline because there are no regular appointments outside your home.	It might be easier to share personal problems on the internet.
Concerns about the safety of exchanging information online.	You can follow the treatment from home.
	It might be easier to seek out for help using a website than by visiting a healthcare organization.

Statistical analyses

The proportion of patients who agreed with each statement (advantages and disadvantages) was calculated for each statement separately and then summed. Group differences were tested using T-tests, Mann-Whitney-U tests and Pearson Chi-square tests where appropriate with a significance level of $P < .05$. The group differences in diagnosis, gender, and age (median split) were calculated with regard to the different advantages and/or disadvantages, importance of therapist contact and other aspects of the internet-based treatment, and willingness to participate (dichotomized into 'not willing to participate under any circumstance' (score 1) and 'willing to participate' (score 2-5) in internet-based CBT).

Results

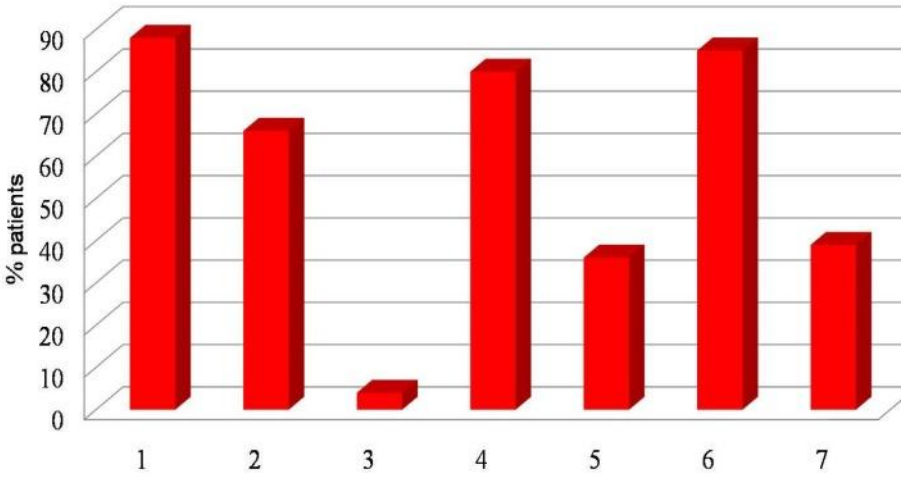
Advantages and disadvantages

The percentage of endorsement of the advantages of internet-based CBT was higher compared to the percentage of endorsement of the disadvantages, when summing up all mean percentages (56% vs. 34%). As can be seen in Figure 1, most participants endorsed the lack of travelling time and costs (88%), being treated at home (85%), and being able to choose the time of treatment (80%) as advantages. Approximately two-thirds of participants endorsed that not having to wait at the office of the therapist (66%) is an advantage. About a third of the participants endorsed the potential ease of seeking help on the internet compared to visiting a healthcare organization as an advantage (39%) and that the anonymity of sharing personal information on the internet is easier (36%). Very few participants (4%) endorsed that not running into an acquaintance at the psychologist's office was an advantage.

Figure 2 shows the percentage of patients endorsing each disadvantage. About half of the participants endorsed that the inability to reach all individuals by internet-based CBT (49%), that there is no face-to-face contact with the therapist (44%), and that participants need some experience with the computer and internet (43%) were disadvantages. Less than a third of the participants endorsed concerns about safety of exchanging information on the internet (31%), the requirement to regularly spend time on the computer (23%), and the need for more self-discipline (15%) as possible disadvantages. Participants with rheumatoid arthritis versus psoriasis did not differ significantly in the proportion of patients who endorsed potential advantages/disadvantages of internet-based CBT. No significant differences for the patients' gender and age were found, with one exception, namely, men considered the lack of travelling time and costs to be an advantage more often than women did (Z=- 2.22, P <.05).

Figure 1

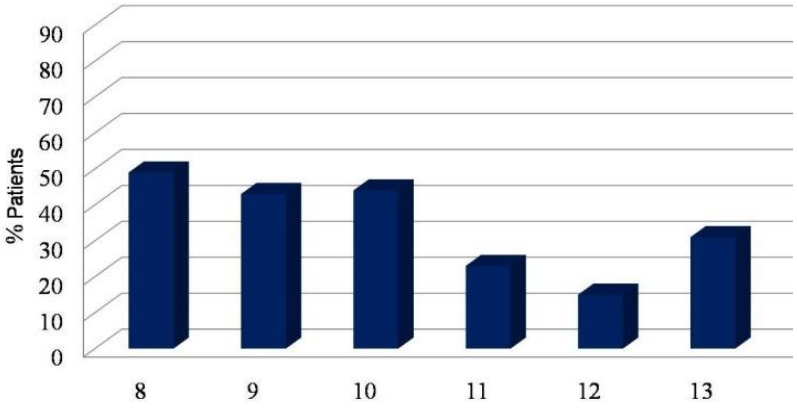
Patients who endorse (%) the advantages of internet-based cognitive behavioural treatment



1. No travel time or travel costs
2. No waiting times before consult
3. No acquaintances encountered
4. Own decision when to spend time on treatment
5. Possibly easier to share personal problems
6. Following treatment at home
7. Possibly easier to seek out for help on the internet compared to visiting a healthcare organization.

Figure 2

Patients who endorse (%) the disadvantages of internet-based cognitive behavioural treatment



8. Not all patients can be reached.
9. Experience with the computer is required.
10. No face-to-face contact with the therapist.
11. Regularly spend time on the computer.
12. More discipline may be needed.
13. Concerns about the safety of exchanging information online.

Therapist contact

A majority of the participants (62%) would like to meet the therapist in person once or twice before starting the therapy, 35% of the participants would like to see the therapist regularly during therapy, and 3% replied they would not want to meet the therapist. When comparing the groups with low (65%) and high (35%) preference for meeting the therapist, no differences were found for diagnostic group (rheumatoid arthritis or psoriasis; $\chi 2=.04$, $P=.83$), gender ($\chi 2=.011$, $P=.92$) or age ($\chi 2=.13$, $P=.72$).

Importance of website aspects

When rating several aspects of the intervention on a 10-point scale, the participants rated a good security on the website (M=8.35; *SD*=2.03), a user-friendly website (M=8.31; *SD*=1.43), and the accessibility of the therapist (M=8.14; *SD*=1.36) as important aspects of internet-based CBT. The lay-out of the website was rated as the least important aspect (M=5.94; *SD*=2.16). Perceived importance of these aspects did not differ significantly by diagnostic group, age, or gender, except that women considered a secure website more important than men did (*P*= 0.03).

Willingness to participate in internet-based CBT

Seventy-eight percent of patients indicated willingness to participate in internet-based CBT under certain circumstances. Nineteen percent of participants would participate even if they did not meet the therapist and 38% if they saw the therapist at least once. A small portion of the patients did not have a preference for internet-based CBT or face-to-face therapy (6%). About 15% of the patients would participate in internet-based CBT, but prefer face-to-face therapy. Twenty-two percent of patients were not willing to participate in any circumstance. The patients' age (median split at 55 years) influenced the willingness to participate (dichotomized; $\chi 2$ (1, 100)=4.15, *P*=.04): younger patients were more willing to participate than older patients.

Differences between patients who do or do not want to participate in internet-based CBT

Participants who would not want to participate in internet-based CBT (22%) endorsed the disadvantages of not seeing the therapist (*Z*=-3.54, *P* <.01), the need to have some experience with internet (*Z*=-2.69, *P* <.01), and having to spend time behind the computer regularly (*Z*=-

5.10, *P* <.01) significantly more often than the participants who would participate. Moreover, participants who would not want to participate in internet-based CBT endorsed the advantages less often compared to those who would participate, except for endorsing no waiting times before the consult as infrequently.

Discussion

When developing innovative treatments for patients, it is important to learn about patients' views and opinions about such treatments [1,2,6]. We assessed the patient perspective of internet-based CBT of patients with rheumatoid arthritis and psoriasis and found that most patients would be willing to receive such treatments, with the endorsement of advantages outweighing the endorsement of disadvantages. Results of this study show that having no travelling time, being able to choose for yourself when you want to participate, and not having to wait for therapists were advantages most often endorsed by patients. Making your own choice about when you want to spend time on therapy could enhance the energy and motivation to participate, but as earlier studies indicate, might also lead to low adherence to the treatment protocol and high dropout rates [5-7].

Face-to-face contact with the therapist is important to patients, with almost half of the patients endorsing that not being able to see the therapist is a disadvantage of internet-based CBT, especially to the group who did not want to participate in internet-based CBT. Accessibility of the therapist was rated as important. A majority of the patients would like to see the therapist at the start of the treatment or at several times during the intervention. This is in line with lower dropout rates and higher adherence in guided E-health treatments [18,19].

Sharing personal information online raises security issues, and participants considered a secure website to be important in internet-based CBT. At the same time, only about a third of the patients endorsed security issues about exchanging information online as a disadvantage. This finding is consistent with literature about online high disclosure behaviour [20]. Furthermore, trust seems to enhance disclosure behaviour online; an internet-based intervention developed by a university hospital might evoke relatively high levels of trust [20].

Disadvantages mentioned by the patients and the opinion of the group who were less willing to participate are important to explore to increase the range of patients E-health could appeal to. Almost half of the patients viewed it as a disadvantage that not everybody could be reached through the internet. Older participants were also less willing than younger participants to participate in internet-based CBT. For healthcare organizations, the older population is known to have more problems with internet usage [21]. Increasing computer literacy, technical support and intervention usability tailored to the older population might aid in solving this problem. Since the current study used a semi-structured interview based on literature reviews, we cannot exclude that other advantages or disadvantages may exist, even though patients did not mention them. Also, for example previous experience with face-to-face treatments and patients' ideas on the ability to tailor E-health treatments could have influenced these results. Future research might further clarify patients' preferences.

In conclusion, patients perceive internet-based CBT as a feasible development and the patient's perspective offers more insight into how the treatments can be improved. To patients, computer literacy and therapist contact are important considerations in E-health and these should be further explored. For the most optimal applicability of the development

and evaluation of internet-based interventions, it is important to incorporate the patients' perspective on these developments during each phase of research.

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Ethics committee

The regional ethics committee of the Radboud University Nijmegen Medical Centre indicated that there was no approval needed for the protocol of this study.

Conflicts or disclosures

None

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Appendix 1

Short explanation of internet-based CBT at the beginning of the interview with patients.

"At this moment we are developing an internet-based treatment for patients with rheumatoid arthritis and psoriasis at the Radboud University Nijmegen Medical Centre. This treatment is aimed at learning to deal with the consequences of the illness for daily life, such as pain and fatigue. We would like to investigate what patients see as important aspects of internet treatments and what they think of several advantages and disadvantages. You could help us gain a better understanding of patients' perspectives."

CHAPTER 4

Measuring the therapeutic relationship in internet interventions.

Authors

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Letter to the editor

The use of the internet for the provision of healthcare is on the rise, with increasing evidence for comparable effectiveness of psychological internet and face-to-face treatments [1, 2]. It is well-known that the quality of the therapeutic relationship during face-to-face treatment contributes at least modestly to an effective treatment outcome [3]. A recent review [4] further suggests that the patient evaluation of the therapeutic relationship in internet-based therapy is comparable to that of face-to-face treatments. However, there might be specific issues of a therapeutic relationship during internet interventions that have been neglected so far. For example, patient evaluations and uptake of internet-based treatments suggest problems in building a therapeutic relationship during internet-based treatments [5]. Internet-based treatments may have incorporated fewer features to develop and maintain a therapeutic relationship as compared to face-to-face treatments. On the other hand internet-based treatments may offer unique characteristics that impact on the therapeutic relationship that face-to-face treatments do not provide [6]. Some studies have indicated that interventions with support of a therapist to motivate patients have lower drop-out rates and may be more effective [7]. Finally, little is known about which patient pre-treatment characteristics contribute to a better therapeutic relationship during internet interventions.

In previous studies on the therapeutic relationship in internet interventions, instruments were used that are commonly used in face-to-face treatment. To our knowledge, no instrument currently exists to measure internet-specific aspects of the therapeutic relationship during internet-based interventions. In this letter we describe (1) the sensitivity to change, and (2) the associations with pre-treatment patient characteristics as well as (3)

patient-reported treatment outcome of an instrument to measure the therapeutic relationship during an internet intervention.

This study reports on data from 98 psoriasis and rheumatoid arthritis patients who participated in the treatment arm of two ongoing trials between July 2010 and May 2014. Patients were asked to fill out a paper and pencil version of the ITRQ together with the Dutch translation of the short form of the Working Alliance Inventory (WAI-S) [8], firstly after an instruction session of the treatment website by a member of the research team, and again at treatment completion. The WAI-S is generally used for assessing the face-to-face treatment alliance. Also, at pre-treatment several questionnaires on general well-being were assessed (see Table 1).A full description of both trials and inclusion criteria participants were drawn from can be found at *http://www.trialregister.nl/trialreg/admin/rctsearch.asp* with trial numbers NTR2100 and NTR2436. Of the 98 patients, 72 pre-treatment and 75 post-treatment measurements of the questionnaire assessing internet-specific aspects of the treatment were available and 52 patients completed both the pre- and post questionnaire. Treatment consisted of an internet-based cognitive-behavioural treatment, tailored to the individual's goals and characteristics as established during one or two face-to-face intake sessions. Patients received online assignments from one to four treatment modules (pain or itch, fatigue, negative mood, or social functioning) and personalized feedback from the therapist. Treatment ended with a relapse prevention module.

The Internet-specific Therapeutic Relationship Questionnaire, or ITRQ, was constructed after a review of the literature on the specific characteristics of internet-based psychological treatments. For an overview of the English translation of the items on questionnaire and results of the factor analysis, see the appendix. A team of psychologists, researchers, and patient research partners aided in the generation of the items and construction of the

questionnaire. The ITRQ contains 9 items, consisting of two subscales of four items each. Because one item was highly associated with both subscales (item 8), this item was not included in either subscale. The first scale, including items on the time lag aspects in the communication and receiving sufficient attention by the E-coach therapist, was termed "Internet-specific Time and Attention" (Cronbach's α = .92). The second scale, including items reflecting the sharing of information with the E-coach therapist and the home as the treatment environment, was termed "Internet-specific Reflection and Comfort" (α = .87); the internal consistency of the total scale was also satisfactory (α = .89).

Sensitivity to change was assessed by paired-samples t-tests, performed on the ITRQ and the subscales. Both the evaluation on the ITRQ and the WAI-S and subscales showed a significant increase for the total and subscales of the ITRQ from pre- to post-treatment (all *p*-values < .05, Eta^2 >.25), with exception of the WAI-S Task subscale which did not show a significant change (*p*-value > .05). These findings support earlier findings on forming and maintenance of a therapeutic relationship in internet-based interventions.

Table 1 gives an overview of associations between pre-treatment assessed patient characteristics and the ITRQ. Specific physical (such as disease severity and pain) and psychological (such as active coping, acceptance and social support) patient characteristics were associated to either pre- and post assessments of the ITRQ. Demographic variables such as age, gender, diagnosis, education level and computer experience were not associated to the ITRQ (all p-values >.05).

To assess whether the ITRQ may be related to treatment outcome, patients were asked to rate their own progress on coping and complaints at the end of treatment and give a general mark on a scale from 1-10 on treatment satisfaction. Pre-treatment ITRQ scores were

significantly associated with more patient-reported improvement in coping and with higher levels of treatment satisfaction. Higher post-treatment scores of the ITRQ were also related to more patient-reported improvement in coping and complaints, and higher patient satisfaction (all *p*-values < .01, see table 1). Results suggest that the ITRQ is a possible predictor of general treatment satisfaction and predict patient-reported improvements. Future research should reveal if the ITRQ also reliably predicts treatment outcome as measured by pre-post assessments.

This study demonstrates the feasibility of the ITRQ as a new measure for internet-specific aspects of the therapeutic relationships and supports earlier findings for the therapeutic relationship as possible predictor for treatment outcome. Future research should replicate and extend findings in other patient samples, possibly reveal which patients need support in dealing with the internet-specific aspects of internet-based interventions and aid researchers and clinicians in their understanding of the therapeutic relationship during internet-based interventions.

Table 1

Pearson correlation coefficients of the Internet-specific Therapeutic Relationship Questionnaire (ITRQ) at pre-treatment and post-treatment with pre-treatment characteristics, patient-reported improvements in coping and complaints, and overall treatment satisfaction.

		Pre-treatment			Post-treatment		
		ITRQ total scale	ITRQ Time and Attention	ITRQ Reflection and Comfort	ITRQ total scale	ITRQ Time and Attention	ITRQ Reflection and Comfort
Pre-treatment patient characteristics							
Physical characteristics	**Disease severity[1]**	.18	.02	.26*	**.24***	.26	.19
	Pain[1]	.02	-.03	.05	**.28***	**.31****	.21
	Fatigue[1]	.25	.22	.22	.02	.09	.06
Psychological characteristics	**Depressive mood[2]**	-.01	-.04	.02	.08	.14	.03
	Anxiety[2]	-.12	-.16	-.08	.18	.20	.17
	Ilnness cognitions[3] Helplessness	.03	-.04	.07	.16	.16	.14
	Ilnness cognitions[3] Acceptance	-.12	-.05	-.15	**-.29***	**-.29***	**-.24***
	Coping active[4]	**.29***	.24	**.27***	.11	.09	.12
	Coping avoidance[4]	.04	-.03	.08	.10	.05	.11
	Social support[2]	**.36***	**.42****	.26	.19	.15	.19
Post-treatment patient-reported outcome							

Improvement in coping[5]	**.34****	.03	**.49*****	**.52*****	**.35****	**.54*****
Improvement in complaints[5]	.14	-.09	.25	**.46*****	**.38****	**.42*****
Treatment satisfaction[6]	-.20	-.00	**-.31***	**-.59*****	**-.46*****	**-.57*****

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < .001$

[1] Physical functioning was measured using patient-reported visual analogue scales ranging from 0 = 'none at all' to 10 = 'extremely'.

[2] Depressive mood, anxiety and social support were measured using corresponding scales of the Impact of rheumatoid arthritis on general health and lifestyle for rheumatoid arthritis and Impact of Skin Disease on Daily Life for psoriasis. Higher scores reflect a more depressive mood, anxiety and social support.

[3] Illness cognitions as measured by the Illness cognitions questionnaire. Higher scores indicate higher levels of helplessness and acceptance.

[4] Coping strategies were assessed using the Utrecht Coping List. Higher scores reflect a higher tendency to use the coping strategy.

[5] Patients reported improvement on 8 (rheumatoid arthritis) or 9 (psoriasis, due to an extra item on itch) consequences of the chronic condition, such as fatigue, pain and negative feelings. Higher scores reflect more improvement in coping or complaints.

[6] Treatment satisfaction was measured on a scale from 1 = 'not at all satisfied' to 10 = 'very satisfied'. Logarithm and reflection was applied to gain a better distribution; negative correlation coefficients on treatment satisfaction therefore reflect a positive association.

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Appendix

Scales and items of the Internet-specific treatment relationship questionnaire (ITRQ) and loadings of the factor analysis.

Instruction

The following statements reflect how you could possibly experience several aspects of the E-coach treatment. We would like to ask you to respond to each statement by stating to which degree you agree with the statement on a scale ranging from 1 to 10, 1 indicates you totally disagree, 10 reflects that you completely agree with the statement.

Response scale

1 2 3 4 5 6 7 8 9 10

Totally disagree — Completely agree

		Factor loading	
	Subscale: Internet-specific time and attention (T&A)	**T & A**	**R & C**
1	I think it is nice to be able to take the time to think about the message that I will send to the E-coach therapist.	**.90**	.64
2	I think it is pleasant that I do not have to respond to messages from the E-coach therapist immediately.	**.83**	.39
8	During the treatment, the E-coach therapist has sufficient attention for my problems and treatment goals.	**.93**	.58
9	My personal problems are taken seriously by the E-coach therapist.	**.89**	.39
	Subscale: Internet-specific reflection and comfort (R&C)		
3	The internet-based treatment makes it easier for me to share personal problems with my E-coach therapist.	.52	**.81**

4	Following the treatment from home allows me to feel more at ease during the treatment.	.40	**.85**
5	I am able to put my feelings and thoughts into words by writing them down and sending them to my E-coach therapist.	.43	**.85**
6	Writing down my feelings and thoughts during the treatment helps me to clarify them.	.55	**.85**
Additional item			
7	From the assignments and messages that I receive from the E-coach therapist, it is apparent that he/she has thought thoroughly about what is important to me at that moment.	.82	.71

Note: The numbers reflect the original order in the questionnaire.

CHAPTER 5

Tailored therapist-guided internet-based cognitive-behavioural treatment for psoriasis and rheumatoid arthritis: Two case reports.

Authors:

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Abstract

Chronic somatic conditions, such as psoriasis, arthritis psoriatica and rheumatoid arthritis, have a large impact on the patients' life. Tailored therapist-guided internet-based cognitive-behavioural treatment (ICBT) has been shown to be effective in improving physical and psychological well-being in these patients. In order to provide an in-depth illustration of the course and content of this novel treatment and to investigate the therapeutic alliance in an online treatment, two cases are presented. After face-to-face intakes, both patients received therapist-guided ICBT tailored to their specific problems and treatment goals. The treatment resulted in improved physical and psychological well-being and these clinically significant improvements were maintained at 6-month follow-up. In addition, the therapeutic relationship was evaluated positively by both patients and increased further during treatment, indicating an adequate therapeutic working alliance in this online treatment. These case reports show that tailored ICBT may contribute to the improvement of care of patients with chronic somatic conditions.

Introduction

Chronic somatic conditions, including chronic skin and pain conditions such as psoriasis (PS), arthritis psoriatica (PsA) and rheumatoid arthritis (RA), have a large impact on the patients and society at large as a consequence of their significant physical and psychosocial impact. Patients with these conditions are confronted with several physical complaints, including pain, fatigue, and itch, as well as psychological complaints such as anxiety and depression, and experience limitations in their daily life functioning [1-4]. PS, PsA and RA are all auto-immune conditions that share specific characteristics with regard to skin problems and pain symptoms. PsA and RA cause inflammatory arthritis in the joints, leading to symptoms of pain, stiffness, chronic fatigue, limitations in daily life functioning, and a diminished health-related quality of life (HRQoL) [5,6]. Fatigue has been identified as a key symptom in patients with PsA and RA and was added to the core outcome set for future studies, highlighting its importance [7-9]. Both PS and PsA lead to skin lesions characterized by red plaques covered with scales. Although there might be some differences with regard to the specific pathophysiological mechanisms, the experienced symptoms and burden of illness is found to be comparable in these patients groups [5,10-12]. With regard to psychological functioning, about 30-40 percent of the patients with chronic skin and pain conditions has elevated distress levels and can be considered at risk for long-term psychological adjustment problems [13-16]. Therefore, a multidisciplinary approach in the treatment of these patients is vital. Psychological treatments, such as cognitive-behavioural therapy (CBT), have shown to be effective as an adjunct to regular medical treatments to improve physical and psychological wellbeing for patients with chronic skin and pain conditions [17-19]. In addition, several studies underline the relevance of individually-tailored CBT interventions that take patient-specific risk and resilience factors into account to

further improve treatment adherence and effectiveness and decrease attrition rates [20-22]. However, since the lack of specialized therapists and time and travel burden for patients limits the implementation of tailored CBT, offering these interventions online might present important advantages [23]. Research shows favorable effects of internet-based CBT (ICBT) for chronic somatic conditions [24-26]. For example, one randomized, controlled trial (RCT) showed that unguided ICBT can improve the quality of life and levels of anxiety in patients with psoriasis, but was limited by high dropout rates [27]. Guided ICBT has been associated with lower drop-out rates and generally higher effectiveness than ICBT without therapist support [28-32]. Therapist-guided ICBT has been shown to be effective for improving psychological outcomes (e.g. anxiety, depression, and distress), disease-specific physical outcomes (e.g. pain, fatigue, disability) and disease-related impact outcomes (e.g. quality of life) [24,26]. These results are similar to those of traditional face-to-face approaches.
The therapeutic relationship has been shown to be an important factor in predicting treatment outcome in face-to-face treatments [33]. Also in online treatments, the quality of the patient-therapist relationship might be related to treatment satisfaction and patient-reported improvements [34,35]. Preliminary evidence suggests that the therapeutic relationship in internet-based treatments is comparable to that of face-to-face treatments [34,36-38]. However, little is known about which factors contribute to a successful therapeutic relationship over the Internet [34]. An internet-based treatment may pose a challenge for developing a good therapeutic relationship, for example due to the absence of any nonverbal cues. On the other hand, patients report specific advantages of internet-based treatment that may contribute to an effective therapeutic alliance, for example the anonymity that makes sharing personal problems easier [39].

The efficacy of a tailored ICBT approach for patients with chronic somatic conditions with a psychological risk profile was studied in two randomized, controlled trials (RCT's) for

patients with PS [40] and patients with RA [41]. Within the current paper, we describe two cases suffering from different diseases in order to illustrate this psychological approach that can be used for a variety of problems that are reported by patients suffering from various chronic somatic conditions including chronic skin and pain conditions such as PS, PsA and RA. Therefore, the selected cases experience problems that are representative of these conditions, including itch-scratch problems, chronic fatigue, physical limitations, and negative mood. The value of case reports is increasingly being recognized in addition to RCT's, as this design incorporates unique features, such as an in-depth description of the course and content of the intervention and the exploration of factors contributing to possible treatment effectiveness [42]. Therefore, the aim of the present article was to provide an in-depth illustration of the course and content of the tailored therapist-guided ICBT with two case reports differing in symptomatology and treatment goals, including challenges and obstacles that might be encountered. Also, the development of the therapeutic alliance in the online treatment will be investigated.

Methods

Procedure

For the two RCT's from which the cases reported here were selected, inclusion criteria were a diagnosis of PS or RA, age ≥ 18 years, and a psychological risk profile (score ≥ 5 for anxiety and/or ≥ 21 for negative mood measured by the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL;[43,44]) or the Impact of Chronic Skin Disease on Daily Life (ISDL;[45]). Exclusion criteria were (1) pregnancy, (2) insufficient understanding of the Dutch language, (3) severe physical or psychiatric comorbidity, (4) current treatment by a cognitive-behavioural therapist, and (5) no access to a computer and internet. After a screening procedure and written informed consent, patients were randomized to the control

group who received standard medical care or the intervention group who received additional ICBT (see for full description of both trials http://www.trialregister.nl/trialreg/admin/ rctsearch.asp trial no. NTR2100 and NTR2436). For these case reports, two patients were selected from the RCT's who were representative for the ICBT treatment with regard to their reported problems, treatment goals and the applied cognitive-behavioural techniques.

Assessments

Assessments were made with validated instruments before treatment, post-treatment and at 6-month follow-up (FU) (for comparability reasons the 3, 9 and 12 month follow-up assessments of the RA trial were not included). See also online supplementary tables for an overview of the used outcome measures for both the PS and the RA patient.

Physical functioning

Fatigue was measured with the 8-item fatigue subscale of the Checklist Individual Strength (CIS;[46, 47]) in both patients. Itch was assessed in the PS patient with the 4-item itch subscale of the ISDL. Pain was assessed in the RA patient with the IRGL pain scale. Higher scores reflect more symptoms of fatigue, itch and pain.

Psychological functioning

For both cases, depressive symptoms were assessed with the Beck Depression Inventory (BDI;[48]) and negative mood and anxiety by their respective scales of the IRGL/ISDL, with higher scores reflecting worse psychological functioning.

Impact on daily life

Role limitations due to physical health problems and emotional problems of the RAND-36 Health Status Inventory were assessed, with higher scores reflecting less impact [49,50]. For the RA patient, the self-care and mobility scales of the IRGL were also administered with higher scores indicating better functioning.

Cognitive-behavioural factors

Cognitive-behavioural factors were assessed including illness cognitions of helplessness and acceptance (Illness Cognitions Questionnaire, ICQ;[51]), social factors including perceived social support (IRGL/IHDL) and stigmatization (ISDL; only for the PS patient), and worrying (Penn State Worry Questionnaire, PSWQ;[52]). In addition, for the PS patient, scratching behaviour was assessed with the subscales conscious scratching and automatic scratching of the ISDL. For the RA patient, passive (resting, retreating, worrying) and active (pain transformation, distraction, reducing demands) pain coping was assessed with the Pain Coping Inventory (PCI;[53]).

Disease-related variables

Disease activity was assessed in the PS patient with the Psoriasis Area and Severity Index (PASI;[54]), with higher scores signifying greater disease severity. The Self-Administered Psoriasis Area and Severity Index (SAPASI;[55]) was also used to measure self-assessed disease severity, with higher scores indicating more severe self-perceived psoriasis. For the RA patient, disease activity was assessed using the self-report measure Rheumatoid Arthritis Disease Activity Index (RADAI;[56]), with higher scores reflecting higher self-reported disease activity. Medical treatment compliance was assessed with a questionnaire asking how often patients adhered to medical treatment prescriptions/recommendations with regard to several aspects of the medical care [57]. Each question could be answered on a 5-point Likert scale, ranging from less than once a week to 7 days a week, or could be

answered as 'not applicable'. Total scores were constructed by calculating the mean of applicable items, with higher scores indicating greater self-reported compliance.

Therapeutic relationship

To assess the quality of the therapeutic relationship, the Working Alliance Inventory short-form (WAI-S; [58,59]) was administered after the two face-to-face intakes and at the end of treatment. A higher score indicates a more positive therapeutic alliance. In addition, the newly developed Internet-Specific Therapeutic Relationship Questionnaire (ITRQ;[35]) was used, with higher scores reflecting a more positive therapeutic alliance.

Patient evaluation

Finally, an evaluation questionnaire was administered post-treatment to assess patients' satisfaction with the ICBT intervention and their evaluation of the user-friendliness of the website on a 10-point scale. Additionally, they were asked to evaluate whether the contact with the therapist was motivating and useful on a 6-point scale.

Data analysis

Post-treatment and 6 months' follow-up scores of the two cases were compared to their baseline scores (pre-assessment) and to scores of normative samples (healthy controls or normative group of PS or RA patients for outcomes that can only be assessed in patient populations). Clinically significant improvement was defined in two ways: 1) showing a change from baseline of more than 0.5 standard deviation (SD), using the SD of the normative sample [60], and 2) showing an improvement from baseline of at least 30%, as recommended by the IMPPACT guidelines for clinical trials [61].

Internet-based cognitive-behavioural therapy (ICBT)

Prior to ICBT, patients were invited for two face-to-face intake sessions with the therapist during which the treatment goals were mutually determined. Hereafter, patients started with the online intervention. The ICBT began with an introductory module during which the specific treatment targets within one or two of the five treatment modules (pain, itch, fatigue and physical limitations, negative mood, and social relationships) were selected based on the pre-treatment assessment and the intake interviews. Next, within the chosen treatment modules a flexible protocol was used consisting of various assignments, such as self-monitoring exercises and psycho-educational texts. The ICBT was designed as a tailored, personalized treatment. The therapist selected assignments and online texts that were most suitable to patients' individual problems, treatment goals, and perpetuating cognitive-behavioural factors, and gave individualized feedback on assignments approximately once a week. In addition, patients could send messages to the therapist at their own discretion. The treatment concluded with relapse prevention and long-term goals (see Figure 1 for a schematic overview of the treatment). The treatment protocol was based on techniques from face-to-face standardized treatment protocols for various chronic somatic conditions [20,22,62,63].

Case Mr. A

Case description Mr. A: 64-year old man with psoriasis

Mr. A, aged 64 years, married, retired, had progressive skin complaints since he was 36 years old, diagnosed as PS. PS is a chronic inflammatory auto-immune skin condition that causes red plaques covered with white scales that are frequently accompanied by itch, fatigue and occasionally pain. The skin condition had a large impact on his daily life. He reported having high levels of itch and in response he scratched a lot. He also scratched as an automatic behaviour unrelated to itch, e.g., as a habit and in stressful situations. This scratching behaviour led to skin damage and an aggravated skin condition which resulted in even more

itch. Thus, a vicious cycle of itch-scratching problems was developed [64,65]. Mr. A also reported feeling depressed and anxious as a result of his psoriasis. He felt helpless in dealing with his skin complaints due to numerous unsuccessful coping efforts. In addition, due to shame with regard to his scratching behaviour, he avoided social activities aggravating his negative mood further. He also found it difficult to accept the unpredictable nature of his condition. This led to a high level of experienced stress and Mr. A reported that this, in turn, negatively affected the psoriasis.

The pre-assessment supported a high level of itch, scratching behaviour, negative mood and feelings of helplessness compared to a norm group (see online supplementary table S1). Based on this assessment and according to the face-to-face intakes in which the treatment goals and specific treatment modules tailored to these goals were mutually determined by the patient and therapist, the ICBT of MR. A consisted of the treatment modules itch and negative mood in achieving the treatment goals of diminishing itch-scratching problems and improving mood. The course of Mr. A's treatment will be described below in order to illustrate different treatment methods of the ICBT in more detail.

Treatment Mr. A

The ICBT for Mr. A consisted of the introductory module, module itch, module negative mood, and the closing module. The patient logged in 47 times, completed 37 assignments (95% of the total given assignments), received 13 messages from the therapist, and sent 11 messages within a period of 5 months (1 week introduction module, 8 weeks itch module, 9 weeks negative mood module, 2 weeks closing module). In addition, one phone call was made by the therapist during the online treatment to clarify a given assignment.

Introductory module

In the introductory module, treatment goals were set. For Mr. A, the most important treatment goals were decreasing itch-scratching problems and improving mood. Because the itch and scratching problems were of central importance and also influenced his mood, the itch module was chosen as a starting point.

Itch module

Several psycho-educational texts and exercises were used to diminish the itch-scratching problems. First, Mr. A started keeping a self-monitoring diary on which, every day at a set time, he recorded the level of itch and the number of times he scratched himself, in addition to recurrent risk situations for itch and scratching. Next, psycho-education about the vicious cycle of itch-scratching problems was provided and exercises to decrease scratching, including habit reversal in which patients learn to replace scratching with incompatible behaviour. Mr. A indicated that the self-monitoring exercises made him more aware of his scratching behaviour and that the incompatible behaviour was helping him controlling his scratching better. Attention was also paid to coping techniques to deal with triggering factors of itch and scratching. For example, since water was a triggering factor for Mr. A's itch, he took shorter showers. Because Mr. A felt very stressed when he experienced itch, psycho-education was provided about the relationship between stress, itch, and scratching, in addition to exercises about stress-relieving strategies, such as itch-relieving thoughts and visualizations. For example, Mr. A began using self-thoughts such as "I can tolerate the itch" and "The itch will go away eventually", which helped him stay more relaxed when the itch increased.

Negative mood module

Given the high levels of stress Mr. A experienced in his daily life and the possible negative effect on his psoriasis, in the negative mood module attention was paid to stress

management. Several methods to deal with stress were offered, e.g., relaxation exercises, distraction, problem solving, and reappraising the situation. Mr. A had access within the website to various audio tracks that contain recorded relaxation exercises (including progressive muscle relaxation, cued relaxation, and visualization exercises). He completed one exercise a day and reported that this had a positive effect on his perceived stress. He was also encouraged to regularly apply relaxing and distracting activities in his daily life, e.g., reading, gardening, cycling, and walking. In addition, cognitive restructuring techniques were applied. Mr. A learned to challenge dysfunctional cognitions such as "It is pointless" and "Nothing is helping" and transform them into more helping thoughts such as "I can manage". After several weeks, Mr. A indicated that he was barely stressed anymore, his depressive feelings were greatly diminished, and he withdrew less from social activities.

Closing module: relapse prevention and long-term goals

Given the progress with regard to the treatment goals, it was mutually decided to end the treatment. The closing module dealt with relapse prevention and further improvement of the attained goals. Mr. A stated that he achieved all of his goals. A relapse prevention plan was formulated by Mr. A, including detecting early signs of relapse (e.g. tension) and preventive actions (e.g. relaxation exercises).

Case Mrs. B

Case description Mrs. B: a 26-year old woman with rheumatoid arthritis

Mrs. B, aged 26 years, living together with a steady partner, started having pain complaints in her wrist and knee one year ago. A few months later, she was diagnosed with RA by her rheumatologist. RA is characterized by inflammation in the joints that frequently leads to functional disability, pain, and fatigue. Mrs. B worked as a dental assistant for 32 hours a week. Pain and fatigue were her most prominent complaints, which limited her daily

activities. She tried to ignore her complaints, rested very little between activities and would spend only a small amount of her time on pleasant activities. Whenever she had relatively few complaints, she was very active to make up for earlier periods of experienced loss of productivity. However, these peaks of activity were generally followed by days of exhaustion. In the long run, this over-exertion pattern had led to an increase of complaints and exhaustion. She also worried a lot about how to deal with her complaints and her limitations. Her worrying and the diminishment of pleasant activities had a negative impact on her mood.

The pre-assessment supported the over-exertion pattern and showed very high levels of pain and fatigue, depressive symptoms, high levels of worrying, and low acceptance compared to a norm group (see online supplementary tables S2). Based on this assessment and according the face-to-face intakes in which the treatment goals and specific treatment modules tailored to these goals were mutually determined by the patient and the therapist, the ICBT of Mrs. B consisted of the treatment modules fatigue and physical limitations and negative mood in achieving the treatments goals of less fatigue and improved mood. Below, the content of the treatment of Mrs. B is described.

Treatment Mrs. B

The ICBT for Mrs. B consisted of the introductory module, fatigue and physical limitations module, negative mood module and the closing module. In total, the patient logged in 45 times, completed 31 assignments (82% of the given assignments), received 20 messages from the therapist and sent 22 messages within a period of about 6 months (1 week introduction module, 10 weeks fatigue and physical limitations module, 7 weeks negative mood module, 3 weeks closing module).

Introductory module

In this module, treatment goals were set. For Mrs. B, the most important treatment goals were improving her level of fatigue and to a lesser extent pain (e.g. better alternation of rest and activity, becoming more aware of limits) and improving her mood (e.g., less worrying, less depressive mood).

Fatigue and physical limitations module

By means of self-monitoring of daily activities and levels of fatigue, pain, and mood, it was revealed to Mrs. B that she went on with activities for a long time without breaks which increased her complaints. In addition, a registration of her daily activities and the amount of energy that each activity costs revealed that she overexerted herself on most of the days. Psycho-education with reading texts was given regarding the importance of balancing activity and relaxation to prevent symptoms from aggravating, in addition to exercises aimed at achieving this balance, e.g. structured planning of daily activities and activity pacing (alternating activity and relaxation, spreading out intense activities), balancing enjoyable, important, and necessary activities. Mrs. B indicated that she profited greatly from planning her activities more carefully, while focusing more on enjoyable activities. Since Mrs. B reported waking up very tired in the morning, attention was paid to sleep hygiene. By keeping a sleep schedule for a few days, Mrs. B learned that her being too busy before going to bed caused her poor sleep quality. She started addressing this problem by implementing more relaxing activities such as reading or taking a bath before she went to bed, which diminished her fatigue complaints in the morning.

Negative mood module

In the negative mood module, psycho-education about coping with worrying and exercises about stress-management strategies was offered. Mrs. B regularly practiced various coping techniques (e.g., planning 15 minutes a day for worrying, distraction, problem solving, and

challenging dysfunctional thoughts). Attention was also paid to increasing the amount of pleasant activities and Mrs. B. was asked to schedule at least one enjoyable activity per day. She was actively involved in this exercise and felt that it improved her negative mood symptoms. In addition, attention was paid to coping with dysfunctional thoughts by using techniques such as cognitive restructuring, problem solving and distraction. Finally, relaxation exercises were provided to help her diminish her worrying further and to create more moments of relaxation in her daily life. In a telephone call, Mrs. B indicated that due to a new job she had no time to practice these exercises at the moment. Therefore, she was offered an audio-cd with the exercises, so she could practice these in the future.

Closing module: relapse prevention and long-term goals

Given the progress with regard to the treatment goals, it was decided to conclude the treatment. In the closing module, attention was paid to relapse prevention and future goals. Mrs. B reported to have reached all of her treatment goals to a large extent. In a relapse prevention plan, she formulated early signs of relapses (e.g., increase fatigue) and preventive actions (e.g., adjust daily planning, include more time for relaxation and pleasant activities).

Results

Patient evaluation

After completing the interventions, both Mr. A and Mrs. B reported that the intervention had been very helpful and rated the overall intervention with a 9 on a 10-point scale. Mr. A reported that he could cope better with the itch, scratched less and had greatly diminished his feelings of helplessness and depression. Mrs. B. reported to be better able to respect her boundaries and stop in time. Her fatigue and pain complaints were greatly diminished, she worried less and her mood was improved. With regard to the internet-delivered aspect of the treatment, both patients evaluated the user friendliness of the website positively (Mr. A: 9; Mrs. B: 10; scale 1-10). Furthermore, specific items of the ITRQ showed that they both reported as important advantages of online treatment that they had the time to think about the message to the therapist (Mr. A: 10; Mrs. B: 10; scale 1-10), it was easier to share personal problems (Mr. A: 8; Mrs. B: 10; scale 1-10), and that writing down their feelings and thoughts helped to clarify them (Mr. A: 10; Mrs. B: 10; scale 1-10). Mr. A also reported as advantage the ease of following a treatment at home and not having to travel to the hospital (Mr. A: 8; scale 1-10). Furthermore, they both stated that the face-to-face intakes were a very important aspect of the treatment (10, scale 1-10). Additionally, they both indicated that the contact with the therapist was very motivating (6, scale 0-6) and useful (6, scale 0-6). Finally, they both indicated a preference for internet-based treatment over other forms of treatment (phone-based, face-to-face) for future treatment.

Pre-post and FU improvements

For Mr. A, with regard to physical functioning, improvements were found for itch and fatigue at post- and follow-up assessments. Also, improvements were found for psychological functioning, including negative mood and depression. The level of anxiety

was diminished at post-assessment, but the score at the FU showed a slight increase. The impact on daily life was at the maximal level at pre-treatment and remained stable during the treatment and at FU. In contrast, the clinician-assessed disease severity worsened slightly between pre- and FU-assessment, suggesting the possible use of more adequate cognitive-behavioural strategies to cope with the symptoms and consequences of the disease. Indeed, the level of helplessness and scratching behaviour decreased. No large differences were found with regard to the level of worrying, which was within the range of healthy controls at all assessment. Also, illness cognitions of acceptance remained overall stable. The level of social support was already high at pre-treatment and the experienced stigmatization low, and these outcomes remained stable. Also, Mr. A. had the maximal score for treatment compliance at pre-, post- and FU-assessment. With regard to the clinical relevance of these results, Mr. A showed improvements of > 0.5 SD on all outcomes at post-assessment and FU, with the exception of anxiety and acceptance at FU. In addition, the improvement from baseline was at least 30% for most outcomes at post-assessment, with the exception of itch, acceptance, worrying and the self-assessed disease severity, and for most outcomes at FU, with the exception of itch, anxiety, acceptance, worrying and the clinician-assessed disease severity (see online supplementary table S1).

For Mrs. B, large improvements were found for the physical outcomes of pain and fatigue (at FU within range of healthy controls). Additionally, the psychological outcomes showed relatively large improvements, including depression, negative mood, and anxiety. With regard to the impact on daily life, self-care and emotional role functioning were at the maximal level at pre-treatment and remained stable, and relatively large improvements were found with regard to her level of mobility and physical role functioning. However, the disease severity of Mrs. B also decreased, which makes it difficult to determine whether these improvements can be attributed to the psychological treatment alone. Nevertheless, the cognitive-behavioural factors at post-treatment indicate that she applied more adaptive pain-

coping techniques, such as distracting and reducing demands, and she also rested more. No changes were found with regard to the pain-coping strategies of transforming pain and retreating. At follow-up, Mrs. B stated she could not complete the pain-coping measures because she did not have pain anymore. In addition, feelings of helplessness diminished, acceptance improved and her level of worrying decreased. Social support was already at the maximal score at pre-treatment and remained stable. Also, the treatment compliance was at a maximal score at all assessment points. With regard to the clinical relevance of these results, Mrs. B showed improvements of > 0.5 SD for most outcomes at post-assessment, with the exception of social support and the pain-coping strategies of retreating, worrying, and transforming pain, and on all outcomes at FU. In addition, the improvement from baseline was at least 30% for most outcomes at post-assessment, with the exception of pain, anxiety, and the pain-coping strategies of resting, retreating, worrying and transforming pain, and for all outcomes at FU (see online supplementary tables S2).

Therapeutic alliance

The results of the WAI (see Table 1) showed that the agreement on treatment tasks and treatment goals was already high after the face-to-face intakes and improved even further during treatment. Also, the emotional bond was established at the maximal level after the face-to-face intakes and remained stable during the online treatment without direct face-to-face contact. In addition, results on the internet-specific aspects of the therapeutic alliance assessed with the ITRQ showed a similar pattern. More specifically, both patients reported that it was clear from the assignments and messages of the therapist that she had thought thoroughly about what is important for them at the moment, that the therapist had sufficient attention for their problems and treatment goals, and that personal problems were taken seriously by the therapist.

Discussion

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Internet-based cognitive-behavioural therapy has been shown to be effective for patients with several chronic somatic conditions. These case reports provide an in-depth illustration of the course and content of a therapist-guided tailored ICBT approach for patients with chronic somatic conditions, such as PS, PsA and RA, and a psychological risk profile. In addition, the development of a therapeutic alliance in an internet-delivered treatment was investigated. For both cases the tailored ICBT approach proved effective. Post-treatment clinically meaningful improvements were found with regard to their physical and psychological wellbeing which remained stable or further improved 6 months after treatment, suggesting that both patients continued to benefit from the treatment. Also, the cognitive-behavioural factors including illness cognitions, social support, worrying and coping strategies showed clinically relevant improvements at post-treatment and follow-up. Furthermore, a successful therapeutic alliance was established for both patients after the face-to-face intakes which further improved during treatment.

Over the last few years, researchers and clinicians have increasingly focused on the importance of tailoring treatment to patients' needs in order to improve treatment efficacy and increase adherence. As psychological distress can influence disease course, adherence and treatment success, it is clinically relevant to select patients with a psychological risk profile [66,67]. Therefore, in our study, only patients with a heightened distress level at risk for long-term adjustment problems were selected for the ICBT. In addition, since incorporating patient preferences may increase treatment satisfaction and lower attrition rates, the specific treatment modules were matched to the outcomes from which the patients suffered most [28]. Finally, based on the cognitive-behavioural factors that were assumed to perpetuate the complaints, specific assignments were chosen within the treatment modules.

For example, for both patients the negative mood module was relevant, but for Mr. A the focus within the module was on diminishing feelings of helplessness and experienced stress, and for Mrs. B on diminishing her worrying and increasing pleasant activities. Although the HRQoL is equally diminished in chronic somatic conditions, such as PS, PsA and RA, it has been argued that different aspects of the disease might contribute to this lowered HRQoL [10]. For example, in PsA and RA it has been suggested that the physical symptoms and fatigue impact the patient mostly, while PS might have a greater impact on mental health (including social functioning) [6, 68]. Mrs. B indeed experienced high levels of fatigue and pain that limited her daily life functioning. Mr. A, however, did not experience limitations in his social functioning and was also mostly impaired in his physical functioning due to the high levels of experienced itch. Nevertheless, the specific factors contributing to a diminished HRQoL in a specific patient needs also to be taking into account when tailoring treatment to specific problems.

The results on the therapeutic alliance support earlier findings on the possibility of successful forming and maintaining a therapeutic relationship in internet-delivered treatments. Since the working alliance at the beginning of treatment can be predictive of treatment outcome, which was also shown in the psoriasis RCT [40], this in an important result. There are various conceptualizations of the therapeutic alliance, but most share three themes: 1) collaborative nature, 2) affective bond between patient and therapist, and 3) ability to agree on treatment goals and tasks [33]. Specific aspects of this ICBT treatment focused on these themes which might have contributed to the development of this adequate therapeutic relationship, including the face-to-face intakes to establish the emotional bond, treatment goals that were mutually determined, the personalized treatment plan, assignments and messages, and regular contact with the possibility for the patients to send messages to the therapist at own discretion. These aspects were indeed highly valued by both patients. Future research is needed to investigate the development of a therapeutic

alliance in internet-based treatments in more detail, for example by including other treatment modalities such as video conferencing and chatting where the verbal cues are not missing.

Several limitations need to be taken into account. The results of the case reports do not prove the efficacy of this tailored treatment, which has been evaluated in the RCT's [40,41]. In addition, it is unclear whether these results can be generalized to a broader population, including patients with physical and/or psychiatric comorbidity. ICBT might only be suitable for patients with chronic somatic conditions with moderate adjustment problems, while a face-to-face treatment is needed for those patients with severe adjustment problems or multimorbidity. Due to the tailored approach and generic treatment modules, this ICBT could also be useful for patients with other chronic somatic conditions, including patients with chronic skin conditions, chronic pain conditions, diabetes, and cardiovascular conditions, but future research is needed to establish that further. Furthermore, future research should aim at delineating the specific mediating and moderating factors of this tailored ICBT. In addition, more research is needed with regard to ways of establishing the clinical relevance of treatment effects.

To conclude, ICBT offers several advantages, such as the absence of traveling time and costs and flexibility in choosing the time of treatment. These case reports demonstrate that a therapist-guided, individually tailored ICBT treatment is feasible and can result in meaningful changes for patients with chronic somatic conditions and a psychological risk profile.

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Conflicts of interests

None

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Appendix

Figure 1. Overview of the therapist-guided, tailored ICBT treatment.

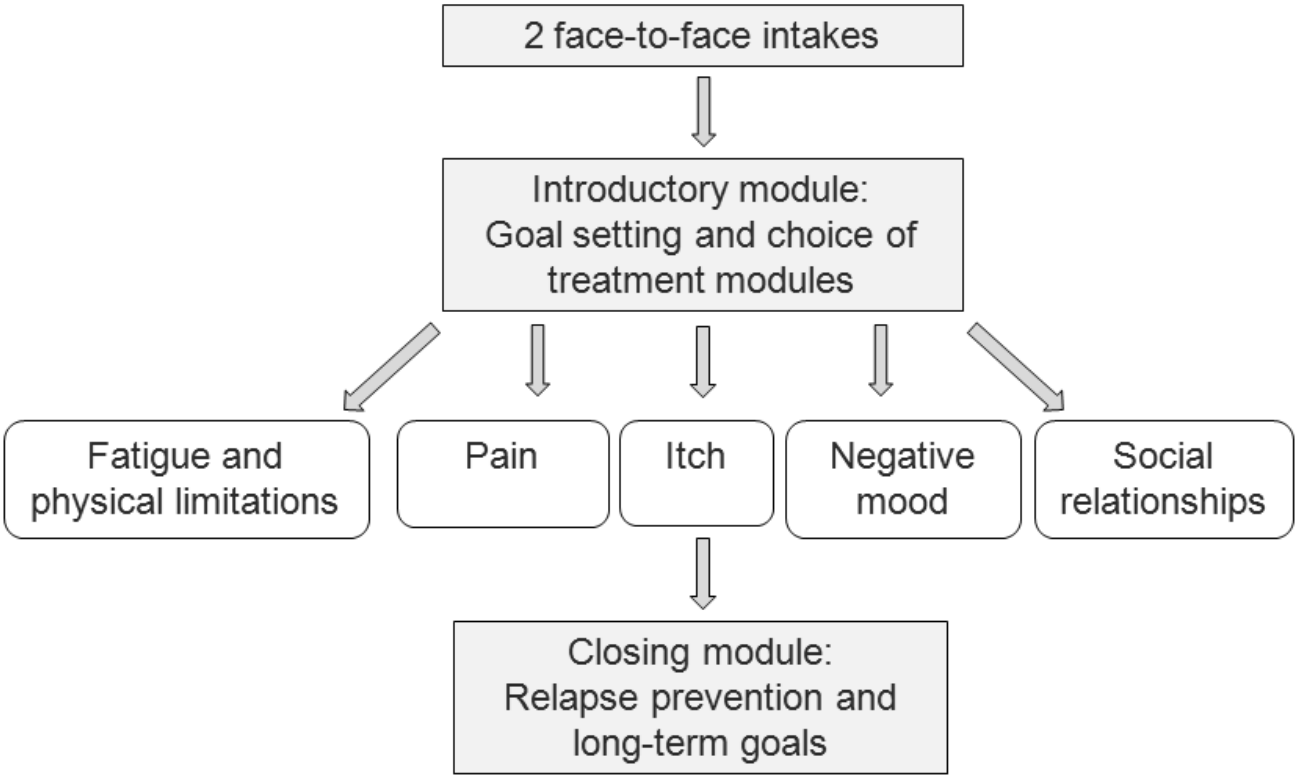

Table 1. Mean scores of Mr. A and Mrs. B at pre- and post-assessment on the therapeutic relationship outcomes including the range of the used measures.

Outcome measures			**Pre**	**Post**	**Range**
Therapeutic relationship (WAI)	Mr. A	Agreement treatment tasks	4.25	4.75	1-5
		Agreement treatment goals	4.50	4.75	1-5
		Emotional bond	5.00	5.00	1-5
	Mrs. B	Agreement treatment tasks	4.75	5.00	1-5
		Agreement treatment goals	4.50	4.75	1-5
		Emotional bond	5.00	5.00	1-5
Internet-specific therapeutic relationship (ITRQ)	Mr. A	Time and attention	10.00	10.00	1-10
		Reflection and comfort	9.00	9.00	1-10
	Mrs. B	Time and attention	9.75	10.00	1-10
		Reflection and comfort	7.75	8.75	1-10

ITRQ = Internet-Specific Therapeutic Relationship Questionnaire; WAI = Working Alliance Inventory short-form.

CHAPTER 6

A tailored guided internet-based cognitive behavioural intervention for patients with rheumatoid arthritis as adjunct to standard rheumatological care: Results of a randomized controlled trial.

Authors

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Abstract

For patients with chronic pain conditions such as rheumatoid arthritis (RA), who experience elevated levels of distress, tailored guided internet-based cognitive behavioural treatment may be effective in improving psychological and physical functioning, and reducing impact the impact of RA on daily life.

A multicenter randomized controlled trial was conducted for RA patients with elevated levels of distress as assessed by a disease-specific measure. The control group (n=71) received standard care and the intervention group (n= 62) additionally received an internet-based tailored cognitive-behavioural intervention. Main analyses were performed using a linear mixed model estimating differences between the intervention and control group in scores of psychological functioning, physical functioning, and impact of RA on daily life at pre- and post-assessment, and at 3, 6, 9, and 12 months.

Patients who received the internet-based intervention reported a larger improvement in psychological functioning compared to the control group, indicating less depressed mood ($p<.001$, $d=0.54$), negative mood ($p=.01$, $d=0.38$), and anxiety ($p<.001$, $d=0.48$) during the course of the one-year follow-up period. Regarding physical functioning, a trend was found for the intervention group reporting less fatigue than the control group ($p=.06$, $d=0.24$), whereas no effect was found on pain. No effects were found for the impact of RA on daily life, except for the intervention group experiencing fewer role limitations due to emotional problems ($p<.001$, $d=0.53$).

Offering guided internet-based cognitive-behavioural therapy is a promising development to aid patients with psychological distress particularly in improving psychological functioning. Further research on adherence and specific intervention ingredients is warranted.

Introduction

In chronic pain disorders such as rheumatoid arthritis (RA), there are often negative consequences in terms of physical and psychological health [12; 22; 26; 37]. Research has shown that cognitive-behavioural interventions can improve both physical and psychological functioning of patients [6; 9; 13; 25; 30]. These interventions are increasingly offered online for reasons of broader implementation possibilities and decrease of travel burden by patients [2; 32]. There is accumulating evidence for the effectiveness of internet-based cognitive behavioural treatments in several domains of psychological and physical functioning [e.g. 2; 4; 11; 32; 40]. Specifically for pain, internet-based interventions have had some mixed results, but effective tailored internet-based interventions have been recently reported [7;8;17;43]. Even though these effects are promising, many questions remain on, for example, the importance of therapist guidance, tailoring to the individual characteristics of the patient, attrition rates, and cost-effectiveness [e.g.1; 3; 14; 28; 35; 38].

Therapist-guided, individually tailored, internet-based cognitive-behavioural interventions for patients with RA with adjustment problems have not yet been reported on. Some evidence exists on internet-based self-management for patients with RA [31; 36; 39]. Those trials that have relatively low levels of support or are peer-guided report positive results on outcomes such as enhanced self-efficacy [31; 36; 39]. Non-guided internet interventions are generally described as less effective and show lower adherence thanguided interventions [1; 35; 38]. It is well-known that there is a substantial group of patients with RA experiencing elevated levels of distress, who are at risk for long-term adjustment problems [e.g. 19; 20] and guided interventions may be especially relevant for these patients. Screening for patients with elevated levels of distress, such as anxiety and negative mood, and tailoring the intervention to their specific adjustments problems may be an important step in improving

the efficacy of internet-based cognitive-behavioural interventions [17; 30; 41]. In addition, when patient preferences are explicitly incorporated from an early stage, for example during the goal setting phase of the intervention, this may further increase intervention satisfaction, which may lead to lower attrition rates [1]. A recent study in pain management offers promising results for such guided tailored interventions [8].

Building upon previous research of our group studying the effectiveness of a tailored face-to-face intervention for RA [21], this study reports on the effects of a randomized controlled trial of an internet-based tailored cognitive-behavioural intervention for patients with RA with a psychological risk profile of elevated levels of distress. It was hypothesized that patients in the intervention group, who would receive internet-based tailored cognitive-behavioural therapy in addition to standard rheumatological care, would show larger improvements in the primary outcome measures of psychological and physical functioning, and a lower impact of RA on daily life, than a control group receiving standard rheumatological care during the study period. As secondary outcomes, effects on patient-reported disease activity and adherence to standard rheumatological care as well as patients' evaluations of the intervention were explored.

Methods

Randomized controlled trial

Effectiveness of the internet-based cognitive-behavioural intervention was investigated by means of a parallel-groups randomized controlled trial (RCT). After a screening procedure (see Procedure) and written informed consent, patients were randomized to one of two study arms. The control group received standard rheumatological care as it is normally conducted in the Netherlands, tailored to the individual with at least yearly check-ups, with

possibly 3 or 6 monthly check-ups to monitor disease activity depending on the general functioning of the patients. Furthermore physical therapy, occupational therapy and care by specialized rheumatology nurses are part of the standard care offered in the Netherlands. The intervention group additionally received an internet-based cognitive-behavioural intervention. The regional medical ethical committee approved the study (NL24343.091.08), which was registered in the national trial registry (NTR2100).

Procedure

Patients receiving standard rheumatological care from rheumatology departments of one academic (Radboud university medical center) and three non-academic hospitals (Rijnstate hospital, Jeroen Bosch Hospital, Medisch Spectrum Twente) in The Netherlands participated. Adult patients with a rheumatologist-certified diagnosis of RA [23] and elevated levels of distress as measured by heightened scores of the negative mood and anxiety scales of the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) [18], were included. Patients were considered to have elevated levels of distress when scoring equal or higher than five on the negative mood scale (6 items, range 0-24) or equal or higher than 21 on the anxiety subscale (10 items, range 10-40) in line with the criteria used in the previous face-to-face trial for tailored CBT in RA [21]. Exclusion criteria were (1) pregnancy, (2) insufficient command of the Dutch language, (3) severe physical or psychiatric comorbidity (i.e. physical or psychiatric comorbidity which required acute and / or intensive medical attention or which was a more impacting condition than rheumatoid arthritis according to the patient view), (4) current treatment by a cognitive-behavioural therapist or comparable practitioner, and (5) no access to a computer and internet. Patients were recruited between the 14th of December 2009 and the 1st of October 2012. The final follow-up assessment was received in December 2013. Patients received an information letter from their rheumatologist or rheumatology nurse and received a telephone call from a researcher to provide further

information, allow patients to ask questions, and to check the in- and exclusion criteria. Potentially eligible patients then received an informed consent form for the screening and completed the screening questionnaire. Patients with elevated levels of distress as determined as mentioned above were invited to participate in the trial. They received further explanation of the trial by phone, and were encouraged to ask questions. After providing informed consent, patients were randomized to either the treatment or the control arm of the study. Patients were randomized to the intervention or control condition by an independent researcher, using a restricted allocation program with minimization was applied (i.e., adaptively stratified) on gender, hospital, education level, age, and baseline patient-reported disease activity (Rheumatoid Arthritis Disease Activity Index, RADAI [24]) to ensure equal distributions across groups. No restriction on patient numbers was applied to ensure no potential foreknowledge of intervention assignment by the research team. An independent research assistant entered the specified data regarding the minimization into the program and communicated the assigned group (control or intervention) to the research team.

Participants

A flow diagram of the total study and of the intervention group specifically can be found in Figures 1 and 2 respectively. A total of 648 participants were assessed for eligibility, of which 563 patients returned screening questionnaires. A total of 198 patients (35% of returned questionnaires) scored at-risk for heightened psychological distress. Of these, 133 patients consented to participate in the RCT: 62 patients were randomized to the intervention group and 71 patients to the control group. See Table 1 for participant characteristics.

Intervention

The intervention consisted of an internet-based cognitive-behavioural intervention tailored to the individual's goals and characteristics. During the face-to-face intake sessions,

therapists explored main issues put forward by the patients and outcomes of the trial pre-treatment questionnaires, and treatment goals were mutually determined. The intervention was further explained and patients and therapists made choices and arrangements on practical issues such as frequency of contact (weekly or biweekly). Hereafter, the internet-based intervention started. Patients completed at least one of four tailored intervention modules (pain and functional disability, fatigue, negative mood, or social functioning). Each treatment module consisted of several assignments and psycho-educational texts. Therapists selected relevant texts and assignments within each treatment module based on the treatment goal and patient characteristics. All four modules contained cognitive strategies such as cognitive restructuring of dysfunctional thoughts, problem solving and goal setting in the light of the somatic condition, applied to the specific subject (e.g., with regard to pain, fatigue, negative mood, and social functioning). Furthermore, the pain module contained cognitive strategies such as identification of pain-provoking cues in daily life and attention diversion, and behaviourally oriented strategies such as activity pacing, stimulation of physical exercise in daily life, and progressive relaxation techniques. The fatigue module contained cognitive strategies such as identification of fatigue patterns, planning and structuring daily activities and relaxation, setting priorities, and cognitive restructuring of activity demands, and behavioural strategies such as activity pacing. Within the negative mood module, cognitive strategies such as emotional processing of RA-related changes during daily life and benefit finding, and behavioural strategies such as increasing the frequency of attainable, pleasurable activities in patients were applied . Lastly, the social functioning module contained cognitive strategies such as the identification of social stress-provoking cues and more behaviourally oriented strategies such as stimulating patients to communicate to relevant others about their RA and its consequences, and training of social skills. Relapse prevention provided to all patients included long-term goal setting by patients

and formulating an action plan in order to prevent relapse in previous cognitions and behaviour [see also 21].

Patients could only access an assignment or text when it was selected for them by the therapist within the treatment environment. The intervention concluded with a relapse prevention and a long-term goals module for all patients. Therapists had weekly to biweekly contact with the patients through a secure e-mail messaging service that was part of the intervention website; patients could respond at their own discretion. Therapist responses typically consisted of empathic reactions regarding personal events described by patients, feedback on treatment assignments, explanation of the rationale for the next assignment and practical tips and encouragement.

The duration of the intervention varied between 9 and 65 weeks (M=26.07, SD=12.22). Twenty-five percent of patients completed the treatment within 17 weeks and 75 percent of patients completed the intervention in 32 weeks. Treatment length varied as the intervention was tailored to patient characteristics and specific goals, and some patients needed more time between assignments, had more goals, or needed more time to practice in daily life. The fatigue and negative mood modules were applied most often (n=37 and 35, respectively), followed by social functioning (n=9) and pain (n=4). Patients mostly worked on the modules consecutively, yet some overlap between modules was possible. Most time was spend on the negative mood module: 10.34 weeks (SD=7.86, range 1-40 weeks), on the fatigue module an average time of 8.95 weeks (SD=5.96, range 1-27 weeks) was spent, on the pain module an average time of 4 weeks (SD=2.94, range 1-7 weeks) was spent and on the social functioning module an average of 3.67 weeks (SD= 2.83, range 1-10 weeks) was spent.

The intervention was provided by six female psychologists with a Master's degree in clinical psychology who had a mean age of 29.67 years (SD=8.76, range 23-46) and an average 2.17 (range 0-7) years of therapeutic experience. A senior clinical psychologist with post-academic training in cognitive-behavioural therapy supervised all therapists.

Measures

The patient evaluation of the internet-based intervention was assessed immediately after completion in the intervention group. All other instruments were assessed immediately after randomization (pre-assessment), immediately following the internet-based intervention for the intervention group and 6 months after pre-assessment in the control group (post-assessment), and at 3, 6, 9, and 12 months follow-up. Patients received a paper and pencil version of the questionnaires at home and were asked to fill these out within two weeks and send them back to the researchers in a pre-addressed and stamped envelope.

Primary outcomes

Psychological functioning

Measures assessing psychological functioning consisted of the Beck Depression Inventory (BDI) [5] and the negative mood and anxiety scales of the IRGL [18]. The BDI consists of 21 items, assessing several aspects of depressive symptoms, in the past two weeks. Each item reflects a particular symptom of depression and comprises of four specific statements regarding the particular symptom (range 0-3). Total scores range from 0-63, higher scores reflect higher levels of depression. Cronbach's α in this study was .87. The IRGL has been developed as a measure for the influence of RA on health and lifestyle. Negative mood is assessed with 6 items reflecting aspects of negative mood (such as feeling depressed, gloomy, disheartened, low spirited, disconsolate or sad) in the past week, with five response

options (range 0=not at all to 4=very much). In this study Cronbach's α = .91. The anxiety subscale consists of 10 items reflecting anxiety in the past week, with 4 response options (1=almost never to 4=almost always). Higher scores reflect higher levels of negative mood and anxiety, respectively. In this study Cronbach's α = .88. A composite score of psychological functioning was calculated, consisting of the standardized scores of these three scales of depressive symptoms, negative mood and anxiety.

Physical functioning

Physical functioning was assessed by the pain scale of the IRGL [18] and the fatigue scale of the Checklist Individual Strength (CIS) [42]. The pain scale of the IRGL (α=.85) consists of six items assessing pain in the past month (1 = almost never to 4 = all the time), disease severity in comparison to previous months (1 = worse, 2 = equal, 3 = an increase), pain intensity (1 = no pain, 5= extremely intense pain), and morning stiffness (1 = no morning stiffness, 5 = morning stiffness for more than two hours). Higher scores reflect higher levels of pain. The fatigue scale of the CIS (α=.85) lets patients self-assess several aspects of fatigue during the past two weeks by means of 8 items on a 7-point Likert scale (1 = yes, that is right, 7 = no, that is not right). Higher scores reflect higher levels of fatigue. A composite score for overall physical functioning was calculated using the standardized scores of the pain and fatigue measures.

Impact of RA on daily life

The impact of RA on daily life of patients was assessed by the self-care and mobility scales of the IRGL [18] and the scales of role limitations due to physical health problems and emotional problems of the RAND-36 Health Status Inventory [27]. The IRGL scale for self-care (α=.91) consists of eight items starting with the preface "I was able to"; items include everyday activities. The IRGL scale for mobility (α=.94) consists of 7 items. Patients are asked

to consider the past four weeks. Answer options for both scales range from 1=almost never to 4=almost always, with higher scores reflecting better functioning. The subscale of the RAND-36 Health Status Inventory on role limitations due to physical health (α=.89) and emotional problems (α=.89) consists of four and three items, respectively, related to being limited with regard to work or other activities as a result of physical health or emotional problems. Patients are asked to assess the past four weeks. Items on both scales are answered with "yes" or "no", which were summed for each scale separately and transformed to a scale ranging from 0 to 100. Higher scores indicate fewer role limitations. The standardized scores of these four questionnaires were used for a composite measure to give an overall impression of the impact of RA on the daily life of patients.

Secondary outcomes

Patient-reported disease activity

Disease severity was assessed using the self-report measure Rheumatoid Arthritis Disease Activity Index (RADAI) [24]. This questionnaire (α=.87) combines five items into a single index: current and past (period of six months) global disease severity, current pain, current morning stiffness, and joint counts of current tender and swollen joints. Higher scores indicate higher disease severity.

Compliance to standard rheumatological care

Compliance to standard rheumatological care was assessed using a patient-reported measure that was designed for this study (α=.75). Patients were asked to rate their compliance to the treatment regimen or advice of their rheumatologist, rheumatology nurse specialist, or other specialists with regard to eight aspects of rheumatological care: general medication, painkillers, physical exercise, activity patterns, use of aids, use of help in the home, support by others (professional care), and other advice with the opportunity to fill out the given

advice. Items could be answered on a 5-point Likert scale, varying from "Always, seven days a week" to "Less than once a week", including the option "Not applicable, I did not receive advice on this subject". Patients were asked to consider the past three months. Compliance scores were calculated by taking the mean of the items that were completed by the patient, with higher scores reflecting higher self-reported compliance.

Patient evaluation of the intervention

Patients in the intervention group rated their overall satisfaction with the internet-based intervention and its user-friendliness on a 10-point scale, with higher scores reflecting higher satisfaction and better user-friendliness. Additionally, on a four-point scale ranging from "no" to "certainly", patients were asked to which degree they thought the intervention would have a sustained positive effect and whether they would recommend the intervention to a friend or family member with a chronic somatic condition. Patients were also asked about their preference for a specific mode of delivery (online, by phone, face-to-face) in case they would need an intervention in the future.

Analysis

As primary outcome measures, total (composite) scores were calculated to assess psychological functioning, physical functioning, and impact of RA on daily life, with higher scores reflecting worse psychological and physical functioning, and a higher impact of RA.on daily life, respectively. These scores were calculated from averaging the standardized scores of the above-mentioned measures within each outcome domain, in which the standardization was based on the mean of the intervention and control groups combined at the pre-treatment measurement. As secondary measures, patient-reported disease activity and compliance to standard rheumatological care were assessed.

Power calculations were based on effect sizes with regard to the primary outcome measures of a previous tailored cognitive-behavioural study in RA and a meta-analysis of cognitive-behavioural interventions in RA [13; 21]. Using analyses of covariance with an α of 0.05 and a Cohen's d effect size of 0.40, two groups of 65 patients would yield a power of .89.

The normality of distributions of all variables was checked (skewness and kurtosis below 1.5) and transformations were applied when appropriate. To compare baseline characteristics of the intervention versus control group and intervention completers versus intervention non-completers, T-tests and chi-square tests were performed.

Intention-to-treat analyses followed by per-protocol analyses were conducted for the main hypotheses. A linear mixed model for longitudinal data (random intercept model) was applied using maximum likelihood estimated differences between the intervention and control group in psychological functioning, physical functioning, and impact of RA on daily life. The pre-assessment score on the particular outcome measure assessed was added as a covariate to the model, in order to correct for any baseline differences between groups. The linear mixed model for longitudinal data was chosen as it maximizes the use of all available data. Also, similar analyses were performed on the secondary outcome measures. Time was included in the model to analyze time trends, including the post-assessment and all follow-up assessments. For all analyses, the linear growth curve model had the best fit and was applied in the final model. For all outcome measures, additional analyses were conducted including all variables included in the randomization process for minimization as separate covariates (gender, hospital, education level, age, and baseline patient-reported disease activity). Sensitivity analyses were conducted using the baseline observation carried forward method. Cohen's d type of effect sizes of between-group differences were calculated using the difference between the means of the intervention and control group, divided by the

pooled standard deviation of the pre-assessment. Furthermore, within-group improvements were calculated by Cohen's d effect sizes for the primary outcome measures and the subcomposites showing (marginally) significant effects to obtain further insight into the size of the changes, by dividing the difference between pre- to post- and follow-up assessments by the pre-assessment standard deviation. Cohen's d effect sizes of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively [10]. To provide insight into differences in the improvement rates of the primary outcome measures on an individual level, for all outcome measures, the percentage of patients showing at least 30% improvement from baseline to the post-assessment, as recommended by the IMMPACT guidelines for clinical trials [16], were compared in the intervention and control groups by means of chi-square tests. Because the IMMPACT guidelines additionally provide a 5-point change on the BDI to represent clinically important change, the analysis was repeated for the BDI using this criterion as well, leading to similar results (data not shown).

Results

Baseline differences between the intervention and control group

Baseline characteristics for the intervention and control groups are reported in Table 1 (demographics) and Tables 2, 3, 4, and 5 (primary and secondary outcome measures). No baseline differences were found between groups on gender, treating hospital, age, education level, or patient-reported disease activity, nor on psychological and physical functioning (all p-values≥.11), except for the intervention group showing significantly less negative mood (p=.03), lower levels of self-care (p=.04) and mobility (p<.05) and a lower impact of RA on daily life (p=.02) than the control group.

Table 1 Patient characteristics at pre-assessment (baseline)

		Control group	Intervention group	Treatment completers	Treatment non-completers	Total group
N (%)		71	62	40	22	133
Gender	**Male**	24 (34)	24 (39)	17(43)	7 (32)	48 (36)
	Female	47 (66)	38 (61)	23 (57)	15 (68)	85 (64)
Education	**Primary**	0 (0)	2 (3)	0 (0)	2 (9)	2 (2)
	Secondary	53 (75)	44 (71)	31 (77)	13 (59)	97 (73)
	Tertiary	18 (25)	16 (26)	9 (23)	7 (32)	34 (26)
Hospital	**Academic**	26 (37)	22 (35)	14 (35)	8 (36)	48 (36)
	Non-academic	45 (63)	40 (65)	26 (60)	14 (64)	85 (64)
Age		57.14	55.45	52.80 (10.21;26-69)	60.27 (10.02;37-81)	56.35
M (SD;range)		(9.36; 34-74)	(10.69; 26-81)			(10.00; 26-81)
Disease activity (RADAI)		3.84	3.31	2.96 (1.90;.48-	3.99 (2.04; .20-	3.59
M (SD;range)		(1.75; 0.40-7.27)	(1.99; 0.20-7.95)	7.06)	7.95)	1.88; 0.20-7.95)

Outcome measures

For all analyses, time did not have a significant effect on the outcome.As a result, all of the presented results represent group differences across all post- and follow-up assessment points.

Psychological functioning

The intervention group reported a larger decrease in anxiety ($F(1,103.76)=11.45$, $p<.001$, $d=0.48$), negative mood $F(1, 101.42)=6.38$, $p=.01$, $d=0.38$) and depressed mood ($F(1, 97.25)=19.48$, $p<.001$, $d=0.54$) than the control group. Also, on the composite score of psychological functioning, the intervention group reported a larger improvement than the control group ($F(1,105.66)=11.89$, $p<.001$, $d=0.55$) (see Table 2).

Physical functioning

A trend was found indicating a somewhat larger reduction in fatigue in the intervention than the control group throughout the year follow-up ($F(1,106.40)=3.5$, $p=.06$, $d=0.24$), whereas groups did not differ on pain ($p=.35$). No significant differences between the intervention and control group were found for the composite score on physical functioning ($p=.17$; see Table 3).

Impact of RA on daily life

The intervention group reported a significantly larger decrease in role limitations due to emotional problems than the control group ($F(1,102.5)=15.17$, $p<.001$, $d=0.53$). The groups did not differ on role limitations due to physical problems ($p=.42$), mobility ($p=.52$) and self-care ($p=.19$). A marginally significantly larger decrease in the composite score of the impact

of RA on daily life was found for the intervention group compared to the control group (F(1,104.19)=2.91, p=.09, d=0.18; see Table 4).

Secondary outcome measures

No significant group differences were found for patient-reported disease activity (p=.79) and compliance to standard rheumatological care (p=.49; see Table 5).

Patient evaluation of the intervention

The average satisfaction with the intervention was 7.44 (SD=1.71) and user-friendliness was evaluated with a mean of 7.09 (SD=1.89). Almost all patients believed to some degree that the intervention would have a sustained positive effect (93% somewhat, probably or certainly) and the majority of patients would recommend the intervention to family or friends with a chronic somatic condition (89% somewhat, probably or certainly). In case patients would need treatment in the future, 55% indicated a primary preference for face-to-face treatment, 39% for internet-based treatment, 3% put internet-based and face-to-face treatment on a shared first position, and 3% preferred treatment by telephone (see Table 6).

Table 2 Differences in measures of psychological functioning between the intervention and control group at all assessment points.[1]

		Timepoint																**Outcome analysis[2]**	
		Pre-intervention			Post-intervention			Follow-up 3 months			Follow-up 6 months			Follow-up 9 months			Follow-up 12 months			Difference between groups over time	
		M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	*p*	*d*
Depressed mood *(BDI)*	Intervention	**11.53**	6.99	57	**8.16**	5.67	46	**9.20**	7.62	33	**7.15**	6.39	27	**8.64**	6.70	26	**8.11**	6.87	27	.001	0.54
	Control	**13.38**	6.46	61	**12.27**	5.97	59	**13.34**	7.38	42	**11.52**	5.71	40	**13.23**	7.43	39	**12.36**	7.38	40		
Negative mood *(IRGL)*	Intervention	**4.07**	2.56	61	**3.25**	2.39	46	**3.85**	3.56	33	**2.70**	3.12	27	**2.81**	2.60	27	**2.93**	3.25	28	.01	0.38
	Control	**5.42**	4.21	66	**4.95**	4.17	58	**6.07**	4.23	42	**5.10**	4.20	40	**5.36**	4.48	39	**4.54**	3.71	40		
Anxiety *(IRGL)*	Intervention	**20.82**	4.85	60	**18.12**	4.13	46	**18.24**	5.13	33	**16.96**	5.31	27	**18.12**	5.24	26	**18.31**	5.44	28	.001	0.48
	Control	**21.40**	4.85	68	**20.61**	4.99	59	**21.42**	5.27	42	**20.89**	5.20	41	**20.54**	5.67	37	**20.06**	5.78	40		
Psychological functioning *(total score)*	Intervention	**0.13**	0.78	60	**-0.60**	0.71	46	**-0.49**	0.98	33	**-0.82**	0.94	27	**-0.64**	0.99	26	**-0.67**	0.99	28	.001	0.55
	Control	**0.11**	0.91	68	**-0.08**	0.91	59	**0.17**	0.97	42	**-0.06**	0.93	41	**0.02**	1.02	39	**-0.14**	1.01	40		

Notes. [1] Reported means and standard deviations are uncorrected; analyses were performed on corrected scores in case of deviations from normality.
[2] Outcome of the linear mixed model for longitudinal data.

Table 3 Differences in measures of physical functioning between the intervention and control group at all assessment points.[1]

		Timepoint																**Outcome analysis[2]**	
		Pre-intervention			Post-intervention			Follow-up 3 months			Follow-up 6 months			Follow-up 9 months			Follow-up 12 months			Difference between groups over time	
		M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	*p*	*d*
Pain *(IRGL)*	Intervention	**14.78**	4.76	57	**14.60**	4.50	45	**14.48**	4.49	33	**14.26**	4.33	27	**15.08**	5.23	26	**14.36**	4.68	25	.35	0.11
	Control	**15.77**	3.88	64	**15.68**	3.73	57	**16.59**	3.43	41	**15.77**	3.44	39	**15.11**	3.89	37	**15.79**	4.13	38		
Fatigue *(CIS)*	Intervention	**35.98**	11.49	61	**32.13**	11.46	46	**30.24**	12.86	33	**29.70**	13.91	27	**34.12**	14.87	26	**32.38**	13.42	28	.06	0.24
	Control	**38.24**	10.06	68	**35.88**	10.71	59	**36.67**	10.84	41	**33.90**	9.95	39	**33.74**	10.87	39	**34.45**	12.43	40		
Physical functioning *(total score)*	Intervention	**-0.17**	1.40	59	**-0.44**	1.44	46	**-0.53**	1.44	33	**-0.60**	1.50	27	**-0.21**	1.79	25	**-0.35**	1.43	26	.17	0.15
	Control	**0.17**	1.21	66	**-0.01**	1.14	58	**0.21**	1.15	41	**-0.02**	0.95	38	**-0.25**	1.19	37	**-0.03**	1.37	39		

Notes. [1] Reported means and standard deviations are uncorrected; analyses were performed on corrected scores in case of deviations from normality.
[2] Outcome of the linear mixed model for longitudinal data.

Table 4 Differences of measures in impact on daily life between the intervention and control group at all assessment points.[1]

Timepoint	Pre-intervention			Post-intervention			Follow-up 3 months			Follow-up 6 months			Follow-up 9 months			Follow-up 12 months			Outcome analysis[2]	
	M	SD	N	**M**	SD	N	**M**	SD	N	**M**	SD	N	**M**	SD	N	**M**	SD	N	*p*	*d*
Self-care *(IRGL)*																				
Intervention	**27.39**	5.72	60	**27.35**	5.94	45	**27.25**	6.53	32	**27.26**	5.79	27	**25.86**	6.39	27	**26.48**	6.32	27		
																			.19	0.05
Control	**25.04**	6.52	66	**24.41**	6.92	58	**24.02**	6.90	42	**26.01**	6.90	40	**26.41**	5.96	38	**26.10**	5.81	40		
Mobility *(IRGL)*																				
Intervention	**22.00**	5.78	61	**22.30**	5.55	45	**21.27**	6.08	33	**22.81**	5.35	27	**21.15**	6.04	27	**21.78**	5.54	27		
																			.52	0.10
Control	**19.82**	6.40	67	**19.37**	6.55	58	**19.80**	6.11	42	**20.33**	6.27	40	**21.50**	5.72	38	**20.85**	6.31	40		
Role limitations physical health problems *(RAND-36)*																				
Intervention	**39.58**	39.94	67	**48.91**	45.02	46	**50.81**	41.07	31	**55.56**	45.11	27	**33.65**	43.56	26	**55.56**	42.37	27		
																			.42	0.05
Control	**26.49**	38.65	67	**33.19**	39.84	58	**31.88**	40.43	40	**36.54**	41.30	39	**41.45**	43.60	38	**45.21**	41.21	40		
Role limitations emotional health problems *(RAND-36)*																				
Intervention	**69.44**	39.91	60	**83.33**	28.76	46	**81.72**	37.36	31	**95.06**	15.20	27	**84.62**	32.97	26	**91.67**	23.35	28		
																			<.001	0.53
Control	**58.82**	46.47	68	**62.15**	45.26	59	**64.17**	44.90	40	**54.70**	42.91	39	**61.11**	42.54	36	**68.33**	41.99	40		
Impact on daily life *(total score)*																				
Intervention	**2.19**	0.72	60	**2.02**	0.70	45	**2.09**	0.82	31	**1.90**	0.65	27	**2.24**	0.75	26	**2.00**	0.66	27		
																			.09	0.18
Control	**2.49**	0.76	67	**2.49**	0.79	59	**2.50**	0.82	42	**2.41**	0.81	39	**2.26**	0.80	37	**2.25**	0.80	40		

Notes. [1] Reported means and standard deviations are uncorrected; analyses were performed on corrected scores in case of deviations from normality.
[2] Outcome of the linear mixed model for longitudinal data.

Table 6 Patient evaluation of the intervention

Patient evaluation				
	M	**SD**	**Range**	**n**
Overall treatment satisfaction	7.44	1.71	1-10	44
User friendliness of the internet intervention[1]	7.09	1.89	1-10	33

n (%)					
	Certainly	**Probably**	**Somewhat**	**No**	**Total**
Believe in a sustained positive effect	9 (21)	21 (48)	11(25)	3 (7)	44 (100)
Recommend to family or friends in the future	15 (34)	14 (32)	10 (23)	5 (11)	44 (100)

Patient preference for treatment mode in future psychological treatment				
n (%)				
Face-to-face	**Internet therapy**	**Face-to-Face & Internet therapy**	**Telephone**	**Total**
21 (55)	15 (39)	1 (3)	1 (3)	38 (100)

[1]This item was added after the first ten patients completed the evaluation form

Secondary analysis

Covariate analyses

Repeating all analyses including the baseline scores of variables used for minimization as separate covariates showed comparable results for all variables, with one exception: including age in the model of the composite score for impact of RA on daily life led to diminishment of the marginally significant effect of group (p=.14).

Per protocol analyses

Patients who did not complete the intervention did not differ at baseline from patients who completed the intervention on the demographic variables gender, treatment hospital, and psychological or medical co morbidity (p-values≥.35). Intervention completers were younger compared to intervention non-completers (p<.001). With regard to the outcome measures of psychological and physical functioning, and impact of RA on daily life, groups did not significantly differ at baseline, except for fatigue and the composite score of physical functioning (both p-values<.001) and for role limitations due to physical health problems (p=.01) and the composite score of impact of RA on daily life (p=.02), indicating better baseline functioning of the intervention completers compared to the non-completers.

All main analyses were repeated for intervention completers. This did not change the results, with the exception that the marginally significant difference found on the impact of RA on daily life became significant (p=.049).

Sensitivity analyses

Repeating all main analyses while replacing missing values with the baseline carried forward, results remained similar to the main outcomes, with the exception that the marginally significant effect on fatigue became non-significant (p=.28).

Improvements within the intervention and control groups

Improvements in the different aspects of psychological functioning were moderate to large in the intervention group (d=0.47-0.89) and none to small in the control group (d=0.05-0.28). For both physical functioning and impact of RA on daily life measures, no to small improvements were found in both the intervention (d=0.03-0.34 for physical functioning and d=0.08-0.39 for impact of RA on daily life) and control group (d=0.03-0.35 and d=0.01-0.32). For the aspect of impact of RA on daily life showing a significant intervention effect, role limitations due to emotional problems, small to moderate improvement was observed in the intervention group (d=0.35-0.56) and no to small improvement in the control group (d=0.05-0.20).

Individual patient analysis

In order to gain insight into individual patient improvement in response to the intervention as compared to care as usual, the percentage of patients in each group showing a change of at least 30% from baseline to post-treatment on each outcome was assessed, in line with the IMMPACT recommendations [16]. Significantly more patients in the intervention group than in the control group improved at least 30% on depression as measured by the BDI (54% versus 26%; p=.004). On all other main outcomes measures, no significant differences in percentage of patients showing a 30% or more improvement between the intervention and control group were found (p-values>.07).

Discussion

The results of this RCT show the potential value of adding a guided tailored internet-based cognitive-behavioural intervention for patients with RA with heightened distress levels (increased anxiety and negative mood) as assessed by a disease-specific measure, specifically for the reduction of depressed and negative mood, anxiety, and role limitations due to emotional problems, compared to standard rheumatological care alone. Results were stable over the course of a one-year follow-up. In addition, the intervention was positively evaluated by participants and they would recommend the intervention to significant others. Taken together, these results demonstrate that this intervention may be a useful addition to regular care for this subgroup, specifically for clinically relevant changes on depression.

The results of this RCT are largely comparable to the results reported for face-to-face tailored cognitive-behavioural treatment trial in patients with RA that the intervention was based upon [21]. Consequently, the internet seems to be a suitable medium to deliver this form of intervention. The current study specifically included patients with heightened distress, specifically anxiety and negative mood, who are deemed at risk for adjustment problems, and showed an significant effect on psychological functioning, in particular, throughout the year after the intervention. Also, clinically relevant individual changes were mainly found for improvements in depression. In combination with depression being prevalent in RA [e.g.26], these findings underscore the importance of psychological screening of patients prior to such an intervention [17; 19]. Psychological functioning was most strongly impacted by the intervention, which may reflect the value of tailoring the intervention to the needs and preferences of the individual patient [35], as patient and therapist mutually chose the negative mood module as a focus of the intervention far more often than the modules of pain and social functioning. The high priority for the treatment

module of fatigue is in line with previous research showing that a substantial number of patients experiences fatigue as an important problem [29]. Because the results only showed a tendency towards a positive outcome on fatigue but no significant effect, further study should be aimed at determining how these effects can be enhanced.

No effects were found for pain and the physical aspects of the impact of RA on daily life, nor for patient-reported disease activity and compliance to standard rheumatological care. Other studies on cognitive-behavioural interventions also have reported mixed findings on physical outcome measures such as pain and physical disability [7,43]. Dealing with pain was not often chosen as intervention goal by patients and therapists, which may reflect that pain is either not the most relevant problem for many patients in the study or that patients do not consider this type of intervention to be the best option to tackle pain. In a study aimed specifically at patients with pain, which included tailoring and therapist guidance, effects were found on pain outcomes [8]. Possibly, physical aspects of functioning in RA, including pain and fatigue, are best targeted by a combination of cognitive-behavioural strategies with physical activity in addition to standard medical care, as this combination has been shown to be effective offline [17].

The tailoring of the guided interventions to a risk group and their personal goals and adjustment problems is a possible strength of this trial. In order to examine the added value of tailoring, future studies should directly compare tailored and non-tailored interventions in RA. Yet, tailoring also has additional challenges for research, for example the variability in treatment length and content complicates standardized assessment of outcomes. The drop-out during the intervention was comparable to other internet-based interventions [e.g. 32; 40], despite tailoring the intervention to patient risk profiles and goal setting. The chosen analyses allow for maximum use of available data and sensitivity analyses performed

suggest that results are fairly robust, though the sensitivity analysis performed has its own limitations such as distortion of means and covariance structure [33]. Even though a further strength of this study includes the representative sample of patients recruited in several hospitals in comparison to online recruitment of patients, this may also have been an obstacle in maintaining patients in the intervention. About a third of patients who dropped out of the trial, stopped due to comorbidity and worsening of symptoms requiring specialized treatment (see Figures 1 and 2), which may be a side-effect of reaching a broader population. This is supported by data showing intervention non-completers reporting worse functioning on physical outcomes, including disease severity, at baseline. Patients who develop co morbidities or who already have higher levels of physical disability may be less willing to participate in an additional online intervention. Future research might focus on more short-term interventions that match the specific needs of these patients. The relatively high levels of drop-out remains a cause for concern (53% of patients in the intervention group and 44% of patients in the control group had dropped out by the end of the trial), especially in light of somewhat more than half of all patients indicated to prefer face-to-face contact in the future. Future studies may shed more light on feasibility and possibly the dose of the intervention needed to achieve effective results as perceived by patients.

In conclusion, this study offers support for the effectiveness of a guided internet-based tailored cognitive-behavioural intervention for patients with RA who have a psychological risk profile as an addition to standard rheumatological care, specifically in the domain of psychological outcomes. Further study on increasing adherence and consideration of specific intervention ingredients is warranted, especially related to tailoring to the specific needs of patients. The current study is a positive step towards the implementation of evidence-based effective online interventions in multidisciplinary healthcare for patients with RA.

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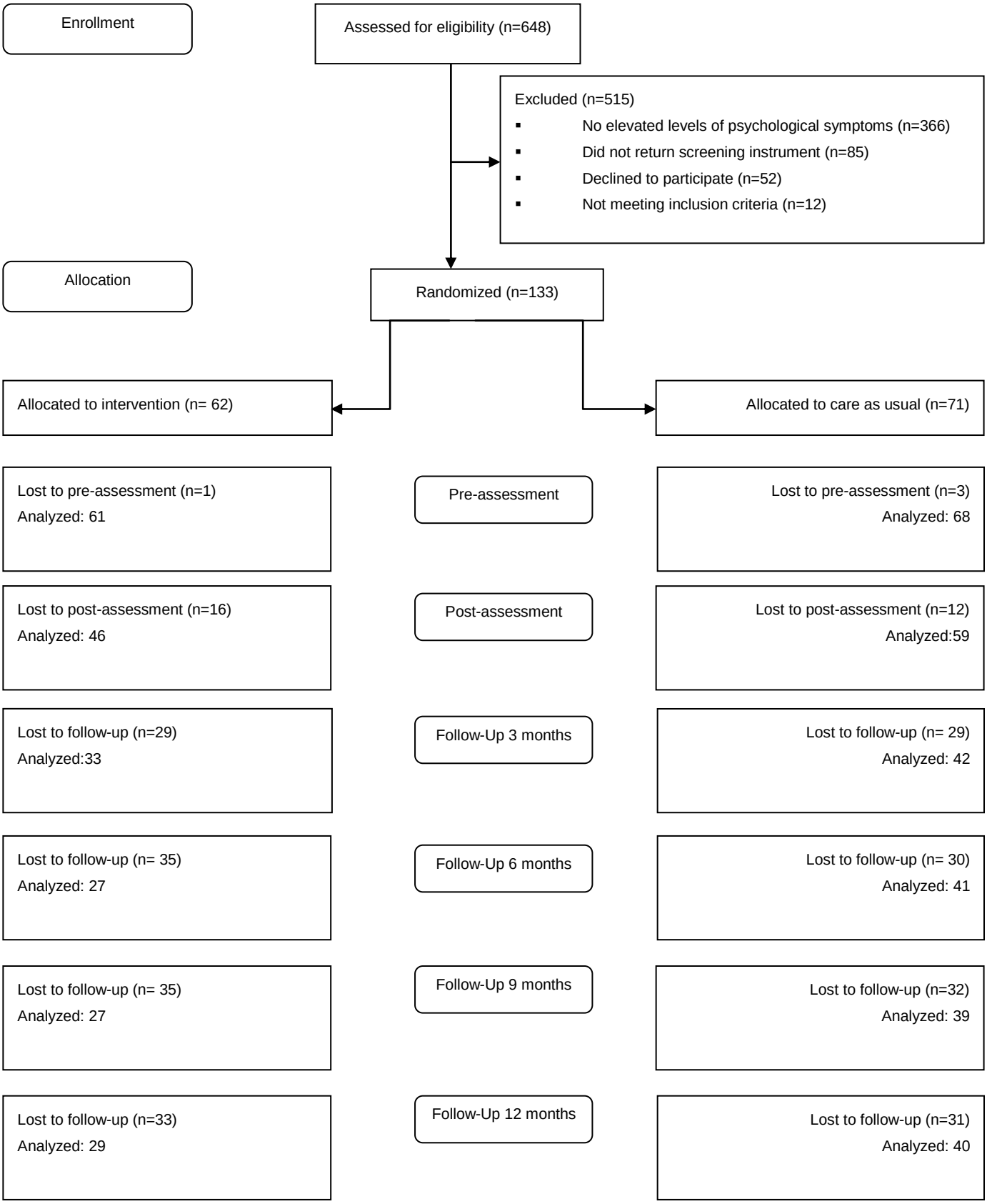
Figures

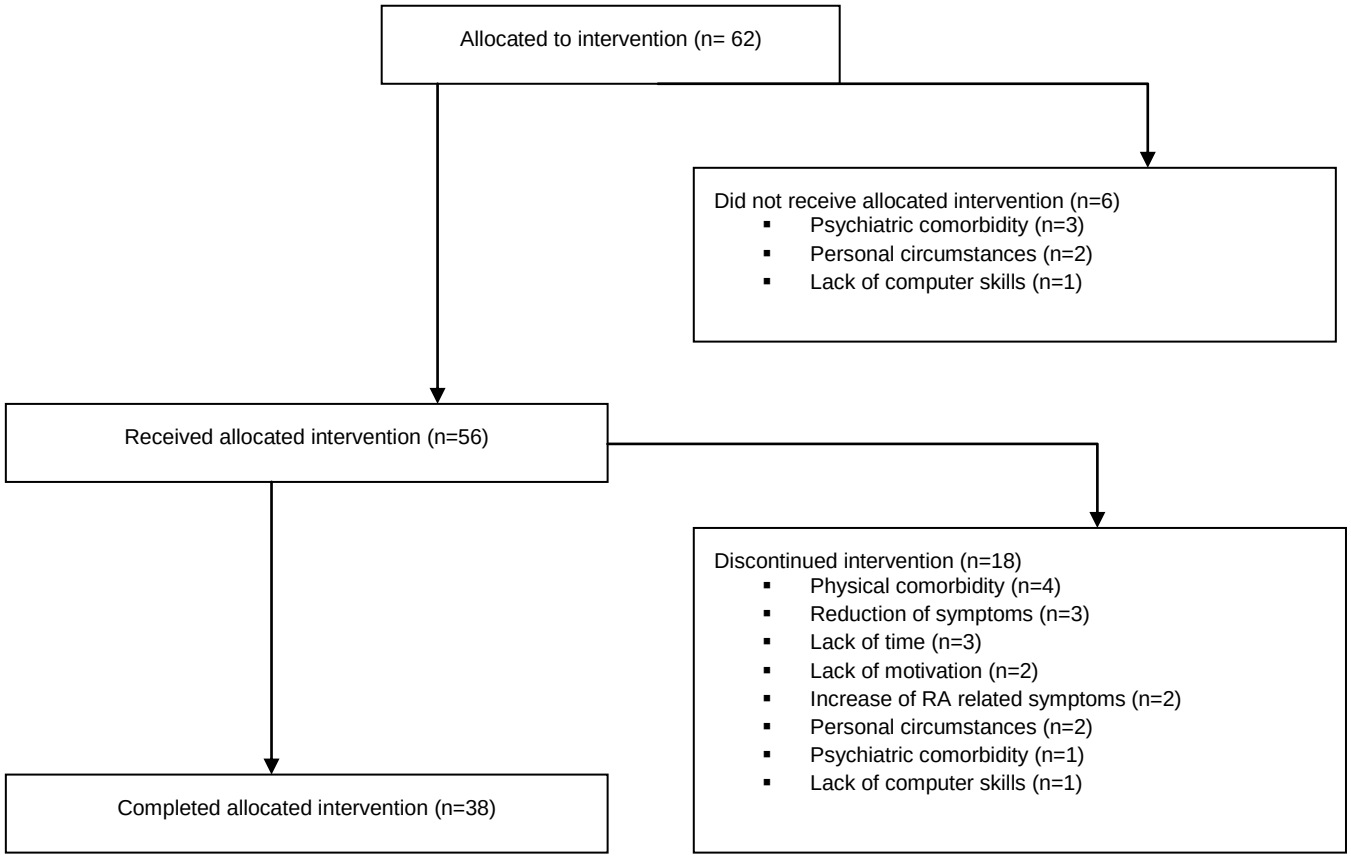
Tailored guided internet-based cognitive-behavioural treatment for patients with RA,

flow-chart of the randomized controlled trial according to Consort criteria 2010.



Tailored guided internet-based cognitive-behavioural treatment for patients with RA

Flow-chart of the intervention group



CHAPTER 7

An economic evaluation of a tailored guided internet-based cognitive behavioural intervention for patients with rheumatoid arthritis as an addition to usual care.

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Submitted

Abstract

Objectives

To stimulate the implementation of effective treatment strategies for improving health-related quality of life (HRQoL) of patients with rheumatoid arthritis (RA), cost-benefit ratios are required to inform stake-holders. A cost-effectiveness study from a societal perspective was conducted alongside a randomized controlled trial on a tailored and therapist-guided internet-based cognitive behavioural intervention (ICBT) for patients with elevated levels of distress, as an addition to usual care alone.

Method

Data were collected at baseline/pre-intervention, 6 months/post-intervention, and three-monthly thereafter during one year follow-up. Effects were measured in quality-adjusted life years (QALYs) and costs from a societal perspective including healthcare sector costs (including healthcare use, medication, and intervention costs), patient travel costs for healthcare use, and costs associated with loss of labor.

Results

The intervention improved quality of life compared to usual care alone (Δ QALYs= 0.059), but also led to higher costs (Δ= € 4.211,44), which reduced substantially when medication costs were left out of the equation (Δ= € 1.862,72). Most (93%) of the simulated ICERS were in the north-east quadrant, suggesting a high probability that the intervention is effective in improving HRQoL, but at a greater monetary cost for society compared to usual care alone.

Conclusions

A tailored and guided ICBT intervention as an addition to usual care for patients with RA with heightened distress was effective in gaining quality of life. Consequently, implementation of the ICBT into standard healthcare for patients with RA is recommended, yet further study into cost reductions in this population is warranted.

Introduction

Within the field of rheumatoid arthritis (RA), the psychological impact of the disease has become increasingly apparent. Patients report decreased health-related quality of life (HRQoL) as a result of living with physical factors such as pain and psychological factors such as negative mood (e.g.,(1-3) As these factors are associated with the disease trajectory, health care utilization, and workplace disability of patients (4-8) these factors lead to significant societal health expenses (9-12).

About one third of patients with RA has been shown to experience a significantly reduced HRQoL (1, 3). For this subgroup, cognitive-behavioural treatment can aid in improving HRQoL (13-15). In a recent randomized controlled trial, we showed a therapist-guided internet-based cognitive behavioural treatment (ICBT) tailored to the specific problems of the individual patient with RA with elevated levels of distress to lead to improvements in especially psychological functioning (e.g., depressed mood) (16). The findings of our study are in line with studies on face-to-face cognitive behavioural treatments (17), which the therapy closely resembles. And add to preliminary evidence that ICBT can be as effective as face-to-face treatments for a range of somatic conditions and symptoms (18-20).

Benefits of internet-based treatments, such as increased flexibility in terms of time and place of following therapy, are suggested to make these treatments feasible for widespread implementation (21, 22) . Evidence on cost-effectiveness of internet-based therapy is still scarce. Preliminary evidence has suggested that internet-based interventions could be a cost-effective way to improve mental health, specifically if guidance by a psychological therapist is offered (23). Within the domain of RA, one study on a self-management intervention for patients with RA-related distress found a reduction of distress and pain, and improved self-efficacy, but no effects on health care utilization (24), which is important in the evaluation of costs. However, no studies on the cost-effectiveness of ICBT in

RA have been conducted up to now. Stakeholders are in need of this kind of information to balance treatment choices and policy decisions. For example, a recent study within the field of rheumatology reports on how rheumatologists balance multiple aspects of a treatment choice, including efficacy, patient preferences, and costs (25).

The current paper reports on a pre-planned cost-effectiveness study from a societal perspective on a tailored and therapist-guided ICBT for patients with RA with elevated levels of distress as an adjunct to care as usual, which was conducted alongside a randomized controlled trial of which the results have been reported elsewhere (16). We predicted the ICBT to be a cost-effective intervention as addition to care as usual.

Method

Design

An economic evaluation from a societal perspective was conducted of a tailored therapist-guided ICBT as an adjunct to care as usual (CAU), alongside a randomized controlled trial (RCT). Patients with elevated levels of distress were either randomized to standard rheumatological care as usually conducted in the Netherlands or additionally to the ICBT. Further details of the RCT can be found in a previous publication on the effects of the ICBT on psychological functioning, physical functioning, and impact of RA on daily life (16). This paper focuses only on aspects relevant to the economic evaluation. All patients provided written informed consent to participation in the study. The regional medical ethical committee approved the study (NL24343.091.08), which was registered in the national trial registry (NTR2100).

Participants

Adult patients with a rheumatologist-certified diagnosis of rheumatoid arthritis (26) receiving out-patient standard rheumatological care at one academic and three non-academic hospitals were invited to participate. Only patients with elevated levels of distress as defined by heightened scores of negative mood (≥ 21 for negative mood on the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) (27) and/ or anxiety (a score of ≥5 for anxiety on the IRGL) were included. Exclusion criteria were (1) insufficient command of the Dutch language, (2) severe physical or psychiatric comorbidity (i.e., requiring acute and /or intensive medical attention. When this was not the case, patients indicated which condition more highly impacted patient's HRQoL), (3) pregnancy, (4) current treatment by a cognitive-behavioural therapist or comparable practitioner, and (5) no access to a computer and internet.

Care as usual and ICBT

Usual care was offered in both the intervention and control group. Hospitals in the Netherlands follow the recommendations of the Dutch Society for Rheumatology for rheumatological care. Usual care for RA patients generally consists of 3- to 6-month shared care check-ups by a rheumatology nurse and the rheumatologist to monitor disease activity and treatment. Additionally, physical therapy and occupational therapy are potentially provided, depending on patient and disease characteristics.

The intervention group received ICBT as an addition to usual care. Aspects of tailoring to treatment goals and individual strategies and therapist contact were important treatment ingredients. Treatment commenced with one or two face-to-face intake sessions consisting of the formulation of individual goals based on the main problems of the patient. Based on these goals, specific treatment modules were chosen embedded within the ICBT website, with the therapist guiding the choice of assignments within each of these modules based on specific risk and resilience factors of the patient. Therapists and patients remained

in weekly or bi-weekly contact within the secured message service within the ICBT website, based on personal patient preferences. Treatment modules focused on coping with 1) pain and functional disability, 2) fatigue, 3) social functioning, and 4) negative mood. Due to the individual tailoring, treatment length varied between 9 and 65 weeks (M=26.07, SD=12.22). All six therapists had a Masters degree in psychology and two additionally had post-academic training in cognitive behavioural therapy. Supervision was provided by a senior clinical psychologist with post-academic training in cognitive behavioural treatment. Patients received one telephone-administered session by a research assistant on how the intervention-website was set-up, which lasted about half an hour. Further information on the ICBT intervention can be found in our earlier publication (16).

Data collection and outcome measures

Data was collected pre-intervention, post-intervention (6-months after the pre-intervention assessment for the control group) and at 3 months (F1), 6 months (F2), 9 months (F3) and 12 months (F4) post-intervention. All costs were calculated based on the 2015 Dutch price indices. In order to correct for biases in non-response, last observation carried forward (LOCF) was applied for missing data.

Effects: quality-adjusted life years (QALYs)

Health-related quality of life (HRQoL) was assessed using the Dutch version of the EuroQol-5dimensions-3levels (EQ-5D-3L) questionnaire (28). The EQ-5D-3L captures five dimensions of functioning in health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three response options: no problems, some or moderate problems, and extreme problems. Utility scores were calculated using the Dutch tariff (28), with scores ranging from 0 (death) to 1 (perfect health). The trapezium rule was applied to calculate the area under the curve for measuring QALYs.

Costs: societal perspective

Costs in this study were calculated for three dimensions: healthcare sector costs (including healthcare use, medication, and the costs of the intervention under study), patient travel costs for healthcare use, and costs associated with loss of labor (absenteeism and presenteeism).

Healthcare use was assessed by the Trimbos/IMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) (29), which was adjusted for healthcare use by patients with rheumatoid arthritis. The questionnaire included patient appointments with rheumatologists, specialized rheumatology nurses, occupational therapists, physical therapists, care by podiatrists, hydrotherapists, admissions to daycare, and inpatient treatment at hospitals or rehabilitation centers. Furthermore, the TiC-P assesses care by the general practitioner and occupational health doctor, psychological/psychosocial care (e.g., care provided by a psychologist, psychiatrist, or social worker), and care provided by alternative medicine practitioners. Costs were calculated by multiplying healthcare use with estimates of unit prices as provided by the TiC-P (29) and the Dutch manual for costs analysis in healthcare (30).

For medication costs, all medication related to rheumatoid arthritis were taken into account including the following: pain medication (including Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), corticosteroids, Disease Modifying Anti-Rheumatic Drugs (DMARDS), and biologics. Furthermore, medication related to psychological symptoms, such as depression and anxiety, and medication related to sleep disorders were taken into account. Medication costs were calculated using the dosages as applied for the type of medication and multiplying these dosages by their costs based on the Dutch national tariff list (www.medicijnkosten.nl).

Costs for the tailored therapist-guided ICBT were calculated by using the actual costs spent on development of the intervention by the ICT-company, salary costs for the therapists (based on the rates for basic psychologists and psychologists with a post-doc training where appropriate) based on the amount of time they spent on the treatment of each patient (including the face-to-face intake sessions, internet-based communication, and additional telephone calls), salary costs for the research assistant conducting the telephone session to explain the intervention website, and patient travelling expenses for the face-to-face intake sessions. An amortization period of five years was assumed. Costs per patient were calculated based on prevalence rates of RA calculated by the Netherlands Institute for Health Services Research (Nivel, 2015). The assumption was made that 30% of the RA-population would be eligible for this intervention due to elevated levels of distress, as was the case in the RCT (16) and in a previous trial aimed at the same target population (17). Of this population size, a population reach of 10% was assumed.

Patient travel costs were calculated by using the Dutch standard for average travel distances from home to several health care services (for example, hospital, GP, physical therapist) in accordance with the Dutch manual for cost analysis in healthcare (30) and multiplying this by a price of € 0.19 per kilometre.

Loss of productivity costs were calculated for the period of a year using the friction costs method including presenteeism and absenteeism, and based on self-reported loss of productivity as reported on the PROductivity and DIsease Questionnaire (PRODISQ(31). The friction period was calculated to a maximum period of 12 weeks (30). For loss of labor, an additional period of four weeks was calculated for management decisions to place the vacancy. Loss of productivity costs were calculated by multiplying the overall average costs of productivity loss per hour (€ 34.90, (30)) by the amount of hours that a patient was absent from work or could not perform optimally at work due to RA.

Statistical analysis

Differences in baseline sociodemographic (e.g., age, gender), disease-related (e.g., disease severity), and economically relevant (e.g., paid labor, healthcare costs, medication costs, HRQoL) characteristics between the intervention and the control group were assessed by using independent samples t-tests or chi-square tests where appropriate.

An incremental cost-utility ratio (ICUR) was calculated to assess the costs per quality adjusted life year (QALY) gained, by dividing the difference in costs by the difference in QALYs. Ninety-five percent uncertainty boundaries on the mean ICUR were determined non-parametrically using bootstrapping (1000 replications). Results of the bootstrap were presented and analyzed by means of a cost-effectiveness plane and willingness-to-pay curve. In line with the Dutch Council for Public and Health Care (RVZ) recommendation that threshold of the incremental cost-effectiveness ratio (ICER) in relation to the acceptability of the treatment has to depend on the severity of the disease with a maximum ICER of 80,000 Euro/QALY (32), the probability that this intervention stays beneath this threshold for willingness to pay is reported. Because the intervention was not primarily aimed at reducing medication costs and a substantial part of the RA patients use expensive biologic agents that strongly influence the cost estimations, a secondary analysis was performed without taking the costs for medication into account.

Results

Information on the number of patients and patient characteristics is given in Table 1. In total, 133 patients were included in the study, with 62 patients in the ICBT-group and 71 in the CAU-group. Measurements at all time-points were filled out by 27% of patients allocated to the ICBT-group and 42% of patients allocated to the CAU group. No baseline differences were found on demographics (all p-values≥.31), disease-related characteristics (p-values≥.11), and cost-or effect-related variables (p-values≥.16). The patient sample was found to be representative of patients with rheumatoid arthritis, with more female than male patients (64 vs. 36%) and a mean age of 56.35 (SD = 10.00; range = 26-81) years.

Between-group differences in effects: QALYs

An overview of the EQ5d utility scores for the intervention and control group can be found in Table 2. Whereas HRQoL was similar for the intervention and control group at baseline (p=.16), the intervention group had a higher QALY score (mean QALY=.86, 2.5 to 97.5 percentile = 0.82 to 0.89) than the control group (mean QALY=.80, 2.5 to 97.5 percentile = 0.76 to 0.83) during the follow-up period of one year.

Between-group differences on costs: societal perspective

For all costs, the intervention and control group did not differ during the one-year follow-up period (all p-values ≥ .32, see Table 3). Total costs for the intervention amounted to € 419,35 per patient.

Table 1 Patient characteristics at pre-assessment (baseline)

	CAU[1]	ICBT and CAU[1]	Total group	Outcome analysis[2] Difference between groups at baseline
N	71	62	133	
EQ5D	.69 (.23; -.11-1.0)	.74 (.19;.09-1.0)	.71 (.21; -.11-1.0)	P=.16
Disease activity (RADAI)	3.84	3.31	3.59	
M (SD;range)	(1.75; 0.40-7.27)	(1.99; 0.20-7.95)	1.88; 0.20-7.95)	
Medical comorbidity	Yes = 36	Yes = 30	Yes = 66	P=.74
	No= 32	No= 30	No= 62	
	Missing = 3	Missing = 2	Missing = 5	
Psychological comorbidity	Yes = 5	Yes = 2	Yes = 7	P=.32
	No= 63	No= 58	No=121	
	Missing = 3	Missing = 2	Missing = 5	
Work status	Paid labor = 28	Paid labor = 28	Yes = 7	P=.59
	Unemployed = 40	Unemployed = 33	No=121	
	Missing= 3	Missing = 1	Missing = 4	
Medication use				
Painkillers	Yes = 8	Yes = 10	Yes = 18	P=.41
	No = 56	No = 46	No = 102	
	Missing = 7	Missing = 6	Missing = 13	
NSAIDS	Yes = 29	Yes = 23	Yes = 52	P=.64
	No= 35	No= 33	No = 68	
	Missing =7	Missing = 6	Missing = 13	
DMARDS	Yes = 52	Yes = 46	Yes = 98	P=.90
	No= 12	No= 10	No= 22	
	Missing = 7	Missing = 6	Missing = 13	
CORTICOIDS	Yes = 13	Yes = 12	Yes = 25	P=.88
	No= 51	No= 44	No= 95	
	Missing = 7	Missing = 6	Missing = 13	
BIOLOGICALS	Yes = 21	Yes = 24	Yes = 45	P=.26
	No= 43	No= 32	No= 75	
	Missing = 7	Missing = 6	Missing = 13	
MENTAL HEALTH MEDICATION	Yes = 6	Yes = 4	Yes = 10	P=.66
	No= 58	No= 52	No= 110	
	Missing = 7	Missing = 6	Missing = 13	

[1] *Note.* CAU = care as usual; ICBT = internet-based cognitive behavioural treatment. [2] Group differences analyzed by chi-square analysis or independent samples t-tests where appropriate.

Results of the cost-utility analysis are presented in Table 2. Incremental effectiveness resulted in an effect of .059. Incremental costs amounted to € 4,211.44 (2.5 to 97.5 percentile = - € 636 to € 9,481). Incremental cost-effectiveness amounted to an investment of € 71,424.82 costs per QALY gained. The cost-effectiveness plane containing a scatterplot of the simulated ICURS is presented in Figure 1a. Most (93%) of the simulated ICURS were in the north-east quadrant, suggesting a high probability that the intervention is effective in improving HRQoL, but at a greater cost for society compared to CAU. Six percent of the ICURS was in the south-east quadrant, suggesting more HRQoL effects at lower costs to society, and 1% of ICURS was in the north-west quadrant, suggesting lower HRQoL effects at higher costs to society (see Figure 1a). At a willingness to pay (WTP) of € 80,000, the intervention has a 57% chance of being cost-effective (Figure 2a).

Repeating the analysis without taking the medication costs into account, the incremental costs reduced to € 1,862.72 (2.5 to 97.5 percentile = - €714 to €5,428). The scatterplot of the simulated ICURS remained about the same (see Figure 1b), but the cost-effectiveness acceptability curve showed a 87% chance of being cost-effective at a WTP of € 80,000 (see Figure 2b).

Table 2. *Quality adjusted life years (QALY) and costs for the internet-based cognitive behavioural treatment plus care as usual (ICBT+CAU) and care as usual (CAU) groups, based on the year follow-up period, indexed to the year 2015, for the primary and secondary analysis.*

Primary analysis

	ICBT+CAU		**Care As Usual**		**Δ QALY**	**Δ Costs**
	QALY	**Costs**	**QALY**	**Costs**		
Average	0.86	€15754	0.80	€ 11542	0.0590	€ 4211,44
2.5 percentile	0.82	€ 8671	0.76	€ 11830	0.007	- € 636
97.5 percentile	0.89	€ 14599	0.83	€ 20134	0.090	€ 9481

Secondary analysis without medication costs

	ICBT+CAU		**Care As Usual**		**Δ QALY**	**Δ Costs**
	QALY	**Costs**	**QALY**	**Costs**		
Average	0.86	€ 4774	0.80	€ 2846	0.0590	€ 1862,72
2.5 percentile	0.82	€ 2541	0.76	€ 1743	0.007	- € 714
97.5 percentile	0.89	€ 7777	0.83	€ 4243	0.090	€ 5428

Table 3. *Mean (±SD) costs in Euros for the care as usual (CAU) and the internet-based cognitive behavioural treatment plus care as usual (ICBT+CAU) groups, based on the year follow-up period, indexed to the year 2015.*

Cost category	**CAU**	**ICBT+CAU**	**Difference between groups**
Health care use	€2548 (3659)	€3252 (8477)	p=.52
Medication use	€8682 (12469)	€10,901 (13257)	p=.32
Patient travel costs	€109 (135)	€151 (160)	p=.93
Absenteeism	€363 (1258)	€1,309 (9106)	p=.89
Presenteeism	€1,800 (5853)	€2,239 (7133)	p=.91
ICBT intervention	*n.a.*	€419,35	

Note. CAU = care as usual; ICBT = internet-based cognitive behavioural treatment, n.a. = not applicable.

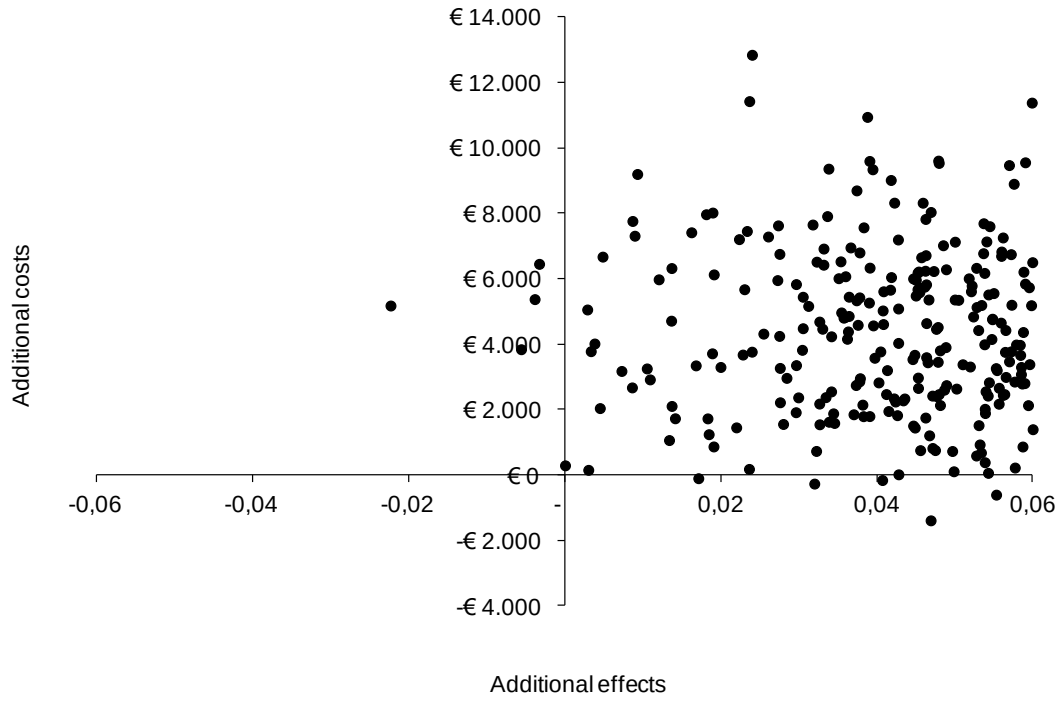

Figure 1a *The cost-effectiveness plane of the simulated ICERs of the ICBT as an addition to CAU.*

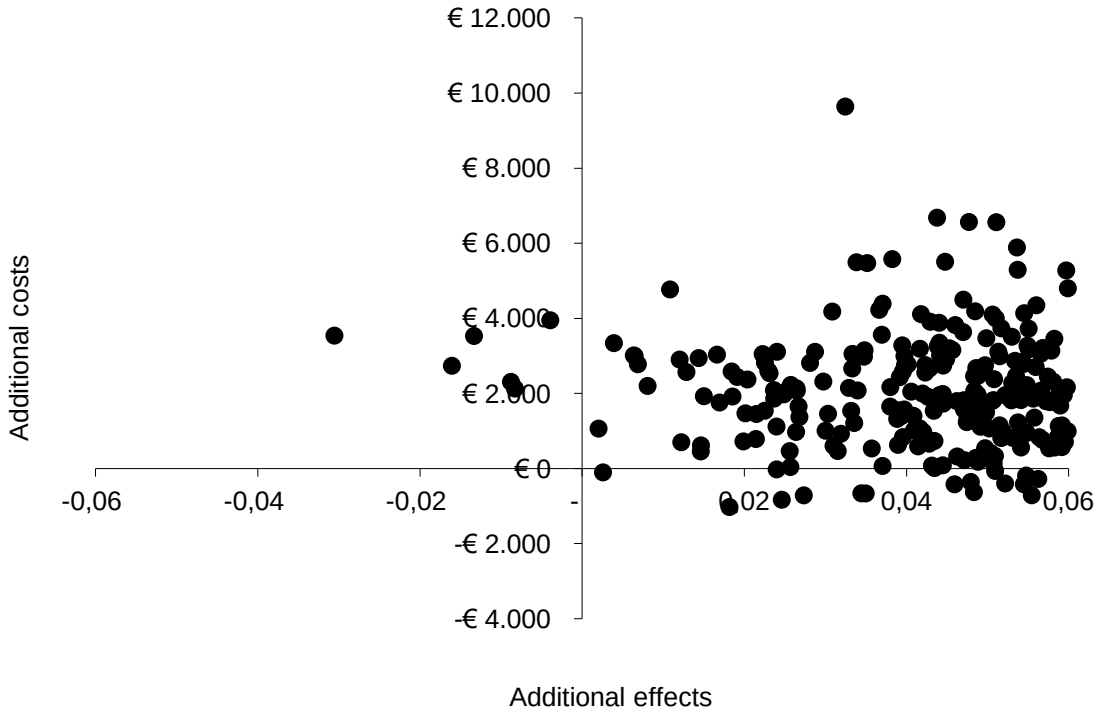

Figure 1b *The cost-effectiveness plane of the simulated ICERs of the ICBT as an addition to CAU without taking costs of medication into account.*

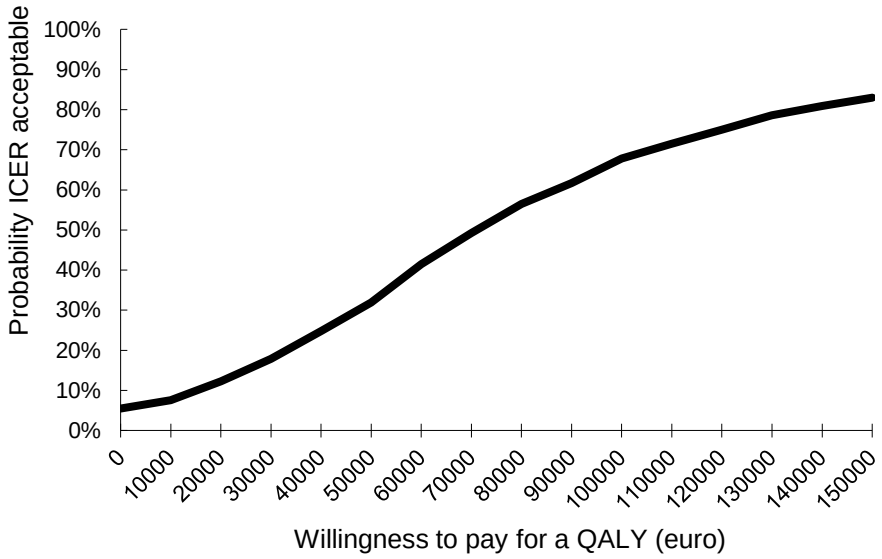

Figure 2a. *Cost-effectiveness acceptability curve comparing for the internet-based cognitive behavioural treatment in addition to CAU (ICBT+CAU) to care as usual alone (CAU) for patients with RA and elevated levels of distress.*

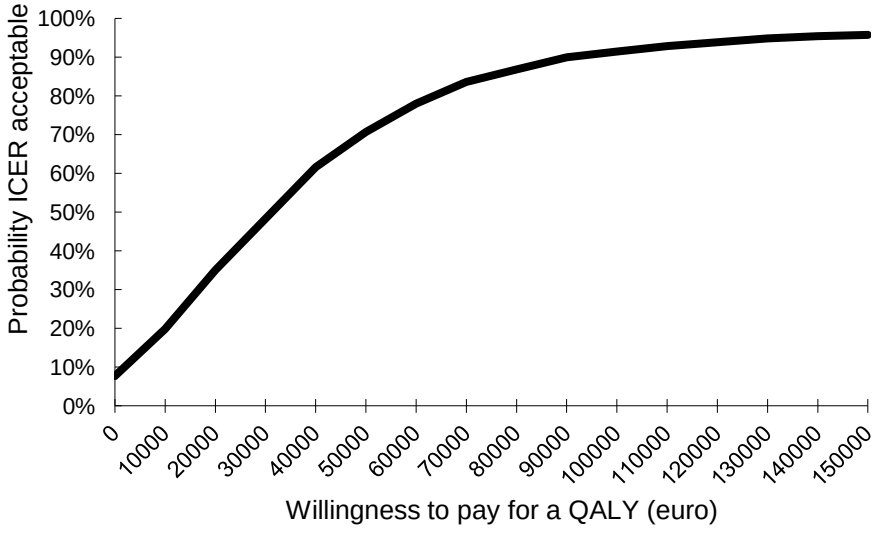

Figure 2b. *Cost-effectiveness acceptability curve comparing for the internet-based cognitive behavioural treatment in addition to CAU (ICBT+CAU) to care as usual alone (CAU) for patients with RA and elevated levels of distress without medication costs taken into account.*

Discussion

This study was conducted in order to get insight into the costs and effects of a tailored therapist-guided internet-based cognitive behavioural treatment for patients with rheumatoid arthritis with elevated levels of distress as an addition to usual care. First, on the side of effects, a positive effect on quality-adjusted life years is seen in the intervention group compared to the control group. Second, cost-ratios show that this comes at a greater cost to society. Third, substantial costs in this population are generated by medication costs, for which no group differences could be found. The cost-benefit ratio improves when the costs for medication are not taken into account. Based on the effects for improvement of quality of life, implementation of the intervention is recommended, yet on the side of costs, further study is warranted.

The current results are in line with earlier studies reporting on promising results of cost-effectiveness in especially therapist-guided psychological interventions (22, 23). Guidance by a therapist comes at a cost, which accumulates with the length of treatment. Reducing therapist time by, for example, using more automated or pre-written responses could be beneficial for costs, with the possible risk of losing the tailored aspects of the intervention. Future research could compare the cost-effectiveness of a guided, partially guided and/or a non-guided intervention to try to find the optimal amount of guidance needed to obtain cost-effective results. The total costs of the intervention per patient were very low in comparison to the other costs accounted for, which makes the intervention a relatively cheap addition to standard care for patients who might profit from this intervention in terms of their health-related quality of life.

Medication costs within the field of RA have received considerable attention as biologics have a relatively high cost, which was also the case in this study. Though in the

past there have been some indications that improved psychological functioning increases medication adherence and lower medication use on the longer term (12), in this study no group differences were found on medication costs. Performing the analysis without medication costs included showed a more beneficial cost-effectiveness ratio of the ICBT intervention. Adherence to medication was not an explicit goal of this intervention. However, it would be worthwhile to examine the ability to change medication adherence and medication use in RA patients by means of internet-based interventions in future studies (33), for example by adding motivational interviewing aimed at adherence (34). Societal gains can also be attained by finding ways to enable patients to participate actively in the workforce [35, 36].

Missing data in this study warrants cautious interpretation of the results, as not all patients filled out all required measurements for the economic evaluation. Even though the last-observation carried forward method was applied for missing values, this can potentially lead to biases in the results.

To conclude, the tailored and therapist-guided ICBT intervention in patients with RA with heightened distress was shown to render higher effects on HRQoL with higher costs, which potentially remain beneath the threshold for interventions in healthcare, especially when costs of medication are left out of the equation. The findings of this study are in support of the implementation of the intervention as a potential addition to usual care for patients with RA with heightened distress, although future study is needed to optimize the cost-benefit ratio.

Acknowledgements and affiliations

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Conflict of interest

None

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CHAPTER 8

English Summary

Summary

Chronic somatic conditions have a large impact on daily life due to both physical consequences such as pain, fatigue and disabilities, and psychological consequences such as worries about the future, negative mood and anxiety. Receiving a diagnosis of a chronic somatic condition requires adjustment; about a third of patients struggle with this adjustment, which has significant consequences for their quality of life. Psychological and physical symptoms interact, and adjustment problems are related to negative consequences for the course of the condition and a lower adherence to medical interventions. In the past, cognitive behavioural therapy for patients with chronic somatic conditions has been found to be effective in reducing physical symptoms such as pain and fatigue, and psychological symptoms such as depression and anxiety. Uptake of these interventions in daily practice is not optimal, due to a lack of trained therapists, travel expenses and difficulties, and accumulation of costs of healthcare in general. To increase availability and dissemination, cognitive behavioural therapy is increasingly offered online. Internet-based cognitive behavioural therapy (ICBT) has successfully been adapted for mental disorders and adjustment problems related to somatic conditions, although the research is still scarce and many questions remain on effective strategies, therapeutic guidance and treatment adherence.

The current thesis aimed to describe the state of the art of internet-based cognitive behavioural treatment for patients with chronic somatic conditions. A systematic review of the effectiveness of trials described in the literature, patient perspectives and the role of internet-bases therapeutic guidance are examined. Moreover, results on (cost-)effectiveness of tailored, guided, internet-based cognitive behavioural treatment for patients with rheumatoid arthritis who experience elevated levels of distress are presented.

Part one: Internet-based cognitive behavioural therapy for patients with chronic somatic conditions.

In **chapter 2** of this thesis, a review and meta-analyses is presented of guided internet-based cognitive behavioural interventions for patients with chronic somatic conditions. An increasing number of trials are being published and systematic evaluation and quantitative analyses could determine whether guided ICBT is effective for chronic somatic conditions. Also, it could provide insight into the types of problems that can be targeted by guided ICBT. Across 23 trials on varying chronic somatic conditions, guided ICBT was found to lead to larger improvements than (passive) control conditions (e.g., care as usual, waiting list) on general psychological outcomes, disease-specific physical outcomes, and disease-related impact outcomes, with the most consistent improvements being found for disease-specific outcomes. Explorative analyses revealed that a longer treatment length could strengthen ICBT's effects for depression. Aside from the positive outcomes, generalizability was found to be limited due to low adherence and high drop-out rates. Nonetheless, guided ICBT was shown to be a promising and effective treatment for chronic somatic conditions to improve psychological and physical functioning and reduce disease-related impact.

As internet-based treatments are generally accompanied by lower treatment adherence and higher drop-out rates than face-to-face treatments, it is important to think of ways to increase adherence. One relevant aspect is suggested to be the incorporation of the patient perspective into newly developed internet-based interventions. Therefore, in **chapter 3,** the perspective of 100 patients with rheumatoid arthritis and psoriasis on the possible advantages and disadvantages of ICBT, as well as their readiness to participate in ICBT, was examined using a semi-structured telephone interview. Patients endorsed the possible advantages such as a decrease of traveling time and costs, choosing when you want to participate and not waiting for the therapist, more often than disadvantages such as computer illiteracy limiting dissemination and not being able to see the therapist. Therapist contact was an important factor to most patients, and most patients were prepared to take part in the internet-based treatment if meeting the therapist at some point during treatment was part of the intervention. In total twenty-two percent of patients were not willing to participate in ICBT, with older patients being less willing to participate compared to younger patients. These patients endorsed not being able to see the therapist

and having to spend time on the computer more often than the patients who were willing to participate in ICBT. The vast majority of patients (78%) were willing to participate in ICBT, which makes it a feasible development.

Because guided ICBT interventions generally show higher levels of adherence and stronger outcomes than unguided interventions and a large body of research supports therapeutic guidance as an important predictor of treatment outcome in face-to-face therapy, the therapeutic relationship may be a relevant factor for treatment retention and outcome in ICBT. The therapeutic relationship is rarely measured during ICBT interventions and, if measured, usually with instruments commonly used in face-to-face interventions. However, unique internet-specific aspects of the therapeutic relationship in internet-based interventions, for example due to asynchronous communication and lack of information on body language, may prove to provide a more complete picture on the relevance of the therapeutic relationship in internet-based interventions. In **chapter 4,** the development and validation of an instrument to measure internet-specific aspects of the therapeutic relationship was described. The (1) structure, (2) convergent validity in relation to a generic measure (the Working Alliance Inventory), (3) sensitivity to change, and (4) associations with pre-treatment patient characteristics as well as patient-reported treatment outcome were assessed. Factor analysis revealed that the 9-item Internet-specific Therapeutic Relationship Questionnaire (ITRQ) reliably distinguishes two aspects: "Internet-specific Time and Attention" and "Internet-specific Reflection and Comfort". Applying this newly developed questionnaire within an RCT examining the effectiveness of ICBT on top of care as usual showed a moderate to strong relationship between the internet-specific therapeutic relationship and the generic therapeutic relationship, indicating the potential to add information on top of the generic measure. The internet-specific therapeutic relationship evaluation significantly increased during treatment, showing sensitivity to change of this new questionnaire. In addition, a higher internet-specific therapeutic relationship evaluation at the start and end of treatment was associated with patient-reported improvement in coping and complaints, and treatment satisfaction, after ICBT. To conclude, the Internet-specific Therapeutic Relationship Questionnaire reliably assesses aspects of the internet-specific therapeutic relationship and could increase our understanding of which internet-

specific aspects are especially relevant to establish a positive therapeutic relationship in internet-based interventions such as ICBT and ultimately reach a beneficial treatment outcome.

Part two: Tailored guided internet-based cognitive behavioural therapy for patients with rheumatoid arthritis and psoriasis with elevated levels of distress

Based on an effective face-to-face CBT for patients with chronic somatic condition and the literature on internet-based treatments as described in Part one, a tailored guided ICBT intervention was developed. In order to provide an in-depth illustration of the content and course of tailored and guided ICBT for patients with a chronic somatic condition and elevated levels of distress, two cases were presented in **chapter 5**. This in depth illustration provides information on how the treatment was tailored to personal goals and how the treatment choices were made based on patient characteristics, providing insight into the role of both patient characteristics and clarifying the role of the therapist in this form of ICBT.

One case described a patient with psoriasis and the other case described a patient with rheumatoid arthritis. After face-to-face intakes, both patients received therapist-guided ICBT tailored to their specific problems and treatment goals. The patient with psoriasis had goals pertaining to itch and negative mood. The patient with rheumatoid arthritis had goals pertaining to fatigue and negative mood. Though for both patients negative mood was part of the focus of the treatment, for the psoriasis patient the treatment was aimed more at stress-management, whereas for the RA patient negative mood was more related to anticipatory anxiety and worrying, and treatment was aimed at this aspect. These cases illustrate that different routes can be taken to attain these goals by tailoring the treatment to personal characteristics and problems. For both patients, the treatment resulted in improved physical and psychological well-being and these clinically significant improvements were maintained up to 6-months follow-up. In addition, the therapeutic relationship was evaluated positively by both patients and increased during treatment, indicating the establishment of an adequate therapeutic working alliance in this specific ICBT intervention. These case reports showed that tailored, guided ICBT may

contribute to the well-being of patients with chronic somatic conditions with elevated levels of distress.

Next to a more in-depth illustration of two specific cases, the effectiveness of tailored-guided ICBT for patients with elevated levels of distress with a diagnosis of rheumatoid arthritis were examined in a randomized controlled trial, reported on in **chapter 6.** Patients with RA were first screened for elevated levels of distress on a disease-specific measure. Those with elevated levels of distress were invited to participate in the RCT. Patients either received standard care or additionally received the ICBT intervention. The patients in the ICBT intervention reported a larger improvement in particularly psychological outcomes, including disease-related anxiety, negative mood and a generic measure for depression. On physical outcomes, no overall improvement was found, although for fatigue a trend was found indicating that the ICBT intervention group experienced less fatigue post-treatment compared to the group receiving standard care alone. No differences were found on the overall impact on daily life, even though fewer role limitations due to emotional problems were reported by the ICBT intervention group compared to the standard care group. Drop-out was relatively high, despite the expectation that tailoring the treatment would lead to less drop-out in this intervention. Besides partially being due to motivational aspects, drop-out may also have been related to characteristics of the broad reach of the current ICBT intervention, because about a third of patients dropped-out due to worsening of symptoms and comorbidity. Despite this important limitation, the intervention was effective in reducing psychological symptoms, and showed clinically relevant improvements in depression in particular. Furthermore, the intervention was evaluated positively by patients, making it a promising intervention option for this patient group.

Of importance to implementation of tailored, guided ICBT for patients with elevated levels of distress is the cost-effectiveness of the intervention. Therefore, a cost-analysis from a societal perspective was conducted alongside the randomized controlled trial. The results of this study are presented in **chapter 7** of this thesis. The intervention improved quality of life compared to usual care alone but also led to higher costs for society, which reduced substantially when medication costs, driven by biologicals that

were already unequally divided between groups at baseline, were left out of the equation. Most of the simulated incremental cost-effectiveness ratios were in the north-east quadrant, suggesting a high probability that the intervention is effective in improving health-related quality of life, but at a greater monetary cost for society compared to standard care alone. Consequently, implementation of the ICBT into standard healthcare for patients with RA is recommended, yet further study into cost reductions in this population is warranted.

The combined results of this thesis lead to clinical recommendations to implement tailored, guided ICBT into standard care for patients with chronic somatic conditions with elevated levels of distress. Nonetheless, further study of adherence, tailoring and therapist guidance is warranted, and evidence needs to be further accumulated to improve cost-effectiveness of such interventions. Future research could aid in establishing essential treatment ingredients and effective strategies. Ultimately ICBT is a promising development to aid patients in achieving a higher quality of life despite having a chronic somatic condition such as rheumatoid arthritis.

CHAPTER 9

General discussion

Discussion

The current thesis aimed to describe the current state of the art on internet-based cognitive behavioural therapy (ICBT) for patients with chronic somatic conditions in general, explored specific topics related to internet-based psychological treatment, such as patient preferences and therapist guidance, and presented the results of a randomized controlled trial into the (cost-) effectiveness of an ICBT intervention for patients with rheumatoid arthritis in particular.

Internet-based cognitive behavioural therapy for patients with chronic somatic conditions

Consequences of chronic somatic conditions can successfully be targeted by ICBT, as the meta-analysis (chapter 2) showed that both psychological impairment and disease-specific outcomes can be improved in a variety of chronic somatic conditions. Effect sizes were found to be modest, especially when general outcomes are used. This is in line with a review on internet-based treatment focused on psychological distress for patients with chronic somatic conditions [1] and earlier comparisons made within the field [2-5]. Disease-specific outcomes showed slightly larger effects, although it is unclear whether this is due to a larger sensitivity to change of specific instruments or due to effects of tailored disease-specific strategies used in these interventions.

Even though the results are promising, the meta-analysis also showed that there is still a limited number of studies published for different somatic conditions, the quality of studies is in need of improvement and little is known on which ingredients are necessary for effects. Treatment length was explored. For symptoms of depression, effect sizes were found to be larger when treatment duration was longer. However, the numbers of studies analyzed were

limited and follow-up measurements were too heterogeneous for a meaningful comparison. Therefore, it remains currently unclear whether in case of longer treatment length effect sizes remain larger over time [1-3].

Aside from a number of limitations of the meta-analysis due to insufficient data reported in the included studies to adequately determine risk of bias and lack of reporting of standard deviations of change, the current meta-analysis specifically focused on RCT's reporting on interventions with therapeutic contact. Up to now, reviews and meta-analyses have consistently shown a superiority in term of effects and adherence of therapist-guided interventions, compared to self-help interventions [1, 4, 6-8], although it is not yet clear which aspects of therapist-led interventions are essential for these effects [9, 10]. In line with other internet-based therapy overviews, adherence and drop-out were also a challenge for the studies in the current meta-analysis, limiting the overall conclusions that can be drawn.

Patient preferences

Before the development of the intervention examined in the second part of this thesis, the patient perspective was explored in semi-structured interviews (chapter 3). Aspects such as saving time and travel were often endorsed advantages. Therapist contact was deemed important and meeting the therapist face-to-face was an important aspect to most patients. Meeting the therapist during the goal setting phase of the intervention, was therefore incorporated in the intervention design. This was also evaluated positively by patients after completion of the intervention (chapter 6).

In the structured interviews on patient views, dissemination concerns were expressed, namely due to concerns on computer literacy. With the rapid growth of the use of mobile devices, growing insight into user-friendly methods [11, 12] and expanding computer

literacy [13], this may not be a major concern in the future, even though it still warrants attention. During the trial, only one patient had severe problems with the use of the website due to limited computer skills and therefore stopped participating in the intervention (chapter 6). Because having an internet connection at home was an inclusion criterion in the trial, computer-illiterate patients were mostly already excluded before partaking in the trial. Although this problem may become less prominent, it is still important to be sensitive to the needs of technological literacy that internet-based treatments have for patients. Therefore, offering the interventions within the context of the healthcare system could be important to make sure patients who are not able to participate in an internet-based intervention are offered a viable alternative, such as face-to-face treatment. About 80% of patients did indicate they were willing to participate in internet-based interventions, although 15% of patients had a preference for face-to-face treatment and around 20% was not willing to participate in internet-based treatment. The exact reasons for this preference needs to be further explored. Recent studies into acceptability of internet-based mental health services, also concluded that a part of the patients still has a preference for face-to-face treatments [14, 15].

A possible route towards increasing acceptability of the interventions is focusing on the user-friendliness of the interventions. User-friendliness of the internet-based intervention was deemed important during the semi-structured interviews, whereas the lay-out of the internet-based intervention was not rated as important by most patients. During the trial, user-friendliness of the intervention was measured. Although on average user-friendliness during the intervention was positively evaluated, improvements may possibly lead to a higher engagement with the intervention. Design-features such as automated dialogue components (simulation of person-to-person interaction) and mediated peer-to-peer communication have been found to be associated with more effective interventions, and may

contribute to a higher level of experienced user-friendliness[16]. Furthermore, although it may not have been deemed as important by patients themselves, the persuasive design literature suggests that people are not always consciousness of their susceptibility to design features, but nonetheless respond better to features that are attractive [11]. Efforts should be made to promote user-friendliness and usability of internet-based interventions to prevent non-adherence and drop-out [11, 16].

Therapeutic guidance

Many aspects pertaining to the role of the therapist were deemed important in the semi-structured interview described in chapter 3. Therapist guidance, meeting the therapist face-to-face and accessibility of the therapist were identified as important factors in the intervention to be developed. This was further supported by the positive evaluation of patients after partaking in the intervention on meeting the therapist during the goal setting phase of the intervention. Moreover, both on the within the context of this thesis developed Internet-based Therapeutic Relationship Questionnaire (chapter 4) and the Working Alliance Inventory (WAI), patients evaluated the therapeutic relationship positively pre- and post intervention. This is in line with other studies, where the therapeutic relationship is often evaluated positively, in face-to-face [e.g.[17-19] and in internet-based interventions [10]. In a related trial for patients with psoriasis, a positive relationship between outcome of the intervention and the evaluation of the therapeutic relationship has been found [20]. These studies add to the literature on the importance of therapeutic guidance within internet-based interventions and show that a positively evaluated therapeutic relationship can be formed and maintained in internet-based interventions.

Therapeutic guidance within internet-based interventions has been associated with improved outcomes [10, 21] and aspects such as adherence [22]. As an addition to the

questionnaires commonly used in face-to-face studies, chapter 4 described the development of a specific internet-based therapeutic relationship questionnaire, the ITRQ. Factor analysis revealed two main subscales, internet-specific time and attention, and internet-specific reflection and comfort. Both pre- and post-intervention measures of the ITRQ were associated with patient reported improvements and patient satisfaction. This study showed the ITRQ to be a feasible questionnaire to be used in future studies. With regard to the subscale internet specific time and attention of the ITRQ, this may an important factor within internet-based interventions as it mainly reflects attention by the therapist in the intervention. Automated dialogue components, meaning a close simulation of person-to-person interactions, have been considered to be an important feature within internet-based intervention design compared to avatars, because patients felt that avatars were a more unrealistic substitute for human interaction[16]. Within the literature on the face-to-face therapeutic relationship, the aspect of the therapeutic bond has not clearly been related to outcomes, while agreement on goals and agreement on treatment strategy were more closely related to predicted outcomes of the interventions [23, 24] . In face-to-face interventions the presence of the therapist is apparent, while in internet-based interventions this is not the case, especially when messages are sent asynchronously. Therefore, measuring factors related to receiving attention and feeling understood despite the physical distance in internet-based interventions, as assessed within the internet-specific time and attention subscale may be especially relevant. The second factor of internet-specific reflection and comfort of the ITRQ is mainly focused on the possibility to take time to reflect and to write down thoughts and feelings. Writing down thoughts and feelings, has been sometimes shown to be effective in reducing emotional distress [25, 26]. Yet, patients may differ in both the ability to reflect and do so in writing, therefore assessing individual differences in the ability of patients to write down their thoughts and feelings may be especially relevant for possible therapeutic outcomes.

Tailoring the intervention

The current literature has provided indications that tailoring of the intervention to the individual patient and therapist guidance are promising for positive treatment outcomes, such as adherence [27]. In our RCT for patients with RA, defining the target population of the intervention and only offering the intervention to this target population was done by using a screening instrument that was used earlier in the face-to-face intervention that the internet-based intervention was based upon. Screening the patients on elevated levels of distress before the start of this intervention resulted in a comparable target group of patients compared to the face-to-face intervention. This screening is also in line with earlier studies that suggest that about one third of patients with rheumatoid arthritis experience higher levels of distress [e.g.[28, 29]. For this patient group, the tailored-guided internet-based intervention may be especially relevant. Within the framework of stepped care, this intervention may be offered to the patients who are not sufficiently helped by psycho-education or a self-help (internet-based) intervention. Yet, in the light of non-adherence, several patients did not complete the intervention, partially due to reasons such as insufficient time or motivation. Screening on psychological distress may be a first step towards tailoring interventions, but is shown not to be sufficient to ensure adherence and motivation.

With regard to ensuring that patients set their own goals of the intervention, which is a second aspect of tailoring, the case studies presented in chapter 5 showed how patients were encouraged to set their own goals and the order of the modules offered to the patients was determined by which goal was of central importance to the patient. Prior to the internet-based intervention, patients received questionnaires and two face-to-face intake sessions; further, personal goals were monitored by the therapist throughout the intervention. The

intervention was completed when patients felt that their goals had been attained, which partially accounts for the large range of intervention length seen in the trial (chapter 6). In the case studies, outcomes were both supported by the patients' own reported goal attainment and by the standardized questionnaires, pre- to post intervention and during the six-month follow-up. Even though this aspect of tailoring is an important strength of the internet-based intervention, and closely related to common clinical practice [30], it also complicated research. Outcomes of the randomized controlled trial were based on the composite scores on three main aspects, psychological functioning, physical functioning and impact on daily life, as all these aspects could be targeted by the internet-based intervention. Yet, not all aspects were equally intervened on, with for example the module targeting pain being rarely used. This probably explains why no differences were found on some specific outcome measures (e.g. pain) and resultantly on composite scores in which these aspects were included (e.g. physical functioning). To improve the randomized controlled trials, either more patients are needed to participate in order to have enough power to be able to establish effectiveness of the intervention. Or the outcome measure could be adjusted to either a patient-reported outcome directly related to each individual's goals at the beginning and at the end of the intervention, and during the follow-up period [31].

On yet another aspect of tailoring, all applied assignments of the therapist are tailored to the specific goals of the patients. This means that only the intervention content relevant to the patient is shown to the patient on the internet website of the intervention. This was done by guiding the treatment modules based on the patients' personal goals, as described above. In addition, also within the modules, assignments were chosen based on the patients' specific characteristics, for example in the choice of which psycho-educational texts are relevant to the specific patient (chapter 5). Furthermore, the messages sent by the therapist contained specific feedback applicable to the patient. As this form of tailoring requires information on

more than one variable, incorporation into this internet-based intervention was done by a therapist. Although this may be achieved by technology in the future, relevant characteristics must be well-identified and measured, in order for automated tailoring to work. In the future, this may further limit therapist-time spend on the internet-based intervention further [16, 32]. However, as the current ICBT intervention was not directly compared to a non-tailored intervention or a non-guided intervention in the current trial, it is not possible to state whether tailoring was essential to the outcomes of this intervention. In addition, drop-out rates from both the intervention and the trial were comparable to those of non-guided and non-tailored interventions [33], although drop-out had multiple reasons and was not clearly related to the intervention design.

Effectiveness of therapist-guided and tailored ICBT in RA

For the target population, rheumatoid arthritis patients with elevated levels of distress, the intervention was found to be effective on outcomes within the psychological domain particularly. When looking more generally across outcome domains, quality of life was shown to be higher in the treatment group post-intervention compared to the control group, as measured by the generic quality of life measure for economic evaluations. These results are comparable to the face-to-face treatment that the current intervention was based upon [34]. Earlier meta-analyses and reviews about psychological treatments in RA (without any tailoring aspects) were mixed [35-38]. As the current form of CBT seems to both affect psychological distress and a decreased impact of the condition on daily life, incorporating it into routine care by offering the internet-based tailored guided treatment into routine care is feasible.

For physical functioning, no differences were found between the ICBT and care as usual groups. However, in relation to fatigue the data indicated that the results were in the right

direction and a larger sample may have led to a significant result, comparable to the results of the previous tailored face-to-face intervention [34] However, the results also might indicate that fatigue possibly needs to be targeted more specifically, or combined with an intervention aimed at physical activity [39, 40]. In contrast to fatigue, pain was rarely a target in the current trial as indicated by patient goals in the treatment group. A recent trial targeting pain with a tailored internet intervention was successful in reducing pain catastrophizing and pain disability, as well as emotional distress [41], and several other internet-based treatments also found positive effects on pain-related outcomes [42, 43]. However, outcomes are mixed [6, 44] and difficult to compare due to the use of heterogeneous outcome measures, designs, target populations and interventions.

Cost-effectiveness

Regarding cost-effectiveness of the intervention, quality of life was found to be enhanced, but does come at a price to society (chapter 7). The intervention seems to come at a relatively low price compared to existing face-to-face psychological interventions [45], although this has to be studied in future studies. Whether society is willing to pay for such an intervention depends on decisions made by policy makers. The costs remain beneath a threshold that was recommended earlier by the Dutch Council for Public and Health Care (RVZ), but this recommendation was made based on treatment regimes aimed at life threatening and severely debilitating conditions.

The current intervention was not aimed at reducing societal costs specifically. Societal costs of RA are related to variables such as medication [46-48], disability costs in the workforce [49-51] and disability [52]. Cognitive behavioural strategies aimed at increasing adherence to medication [53-55] and targeting patients within the workforce [56, 57] have led to positive outcomes in the past. Incorporating such strategies into the current intervention could lead

to a more cost-effective intervention. Also, in an earlier study with a follow-up period of five years, positive results were seen on lower costs of medication [58] and a longer follow-up period of the ICBT intervention examined in this thesis may show comparable promising effects in the long-term.

Clinical implications

Tailored, guided- internet-based therapy for patients with rheumatoid arthritis who experience elevated levels of distress is an effective treatment for the reduction of psychological symptoms such as depression and anxiety, as well as a reduction of the impact of the disease on daily life. Offering the treatment through the internet is feasible, including internet-related advantages such as saving travel and time, which are of importance to patients. The instrument used to screen patients for elevated levels of distress could be implemented into routine rheumatology care, to match needs for treatment and to refer patients to possible care options.

As face-to-face treatments are not feasible to implement on a large scale and dissemination can be greatly improved by internet-based interventions, encouraging health professionals and patients to participate in these types of interventions could be important. The implementation of internet-delivered care in the Netherlands and other countries is currently relatively low [59]. Possible routes to increase both health professionals and patient motivation for internet-based interventions include increasing the familiarity with internet-based interventions [60] , implementation of effective interventions [61], optimizing information about the internet-based interventions and making the interventions both credible and easy to use [15, 61-65].

Another improvement that warrants attention, is that the intervention was designed before the steep increase of mobile devices and was therefore not suited to use as an application on, for example, tablets and mobile phones. Updating interventions to current and rapidly developing technological advances is important, but also a challenge within the view of healthcare and costs [66]. Incorporating design features that motivate people and make the interventions easier to use, are gaining attention [11]. In the future, finding ways to specify tailoring to patient preferences and fine-tuning therapist online encouragements could be beneficial and warrants further investigation.

Strategies to prevent drop-out need to be further disentangled in clinical practice. In the current study, drop-out occurred for a variety of reasons, including a decrease of psychological distress prior to the intervention, and an increase of physical co-morbidity and RA-specific symptoms, personal circumstances, and a lack of motivation and time during the intervention (chapter 6). Drop-out due to decrease of symptoms before the start of intervention could be due to spontaneous recovery. The use of repeated screening moments might help to check for longer-term adjustments problems and include only those patients who do not spontaneously recover. An increase in physical problems is difficult to foresee and in daily practice these patients would probably participate at a later stage when physical problems have decreased. Motivational aspects could be targeted by the afore mentioned improvements of the user-friendliness of the intervention. A recent development is motivational interviewing [67, 68], which could be integrated into the intervention and perhaps be applied by the specialized rheumatology nurses the patients see on a regular basis.

Stepped care has received increasing attention within the domain of healthcare in the past decade, as a means of increasing efficiency and increased access to healthcare [69] and has

been suggested to reduce costs [70]. Typically, patients first receive a low-intensity evidence-based treatment and, when treatment response is not sufficient, the intensity of treatment is intensified by means of one step at a time. At the first step, patients receive information on self-management in combination with information on the healthcare problem. At the second step, a highly standardized self-management intervention is offered to patients, through which they can guide themselves. At a third stage, tailored and guided internet-based treatment is offered, which is the main target population of the internet-based intervention described in this thesis. At the fourth stage, tailored and guided face-to-face treatment is offered to patients for whom the first three stages are not sufficient. We have tested specific criteria for stage 3 in this thesis, showing that patients with RA who have heightened levels of psychological distress can profit from ICBT. Comparable studies should be conducted for the other steps to identify which step would provide the best fit for a specific individual's problems and characteristics. Finally, all stages of the stepped-care model might be incorporated into the healthcare system, including cut-off criteria to assess which step should be offered to which patients.

Research implications

The studies presented in this thesis warrants further research into internet-based interventions for patients with chronic somatic conditions. Perhaps most important, studies on effectiveness and cost-effectiveness on internet-based studies should be conducted on a larger scale in order for evidence to accumulate. Meta-analyses conducted within the field are complicated due to the lack of reporting of all relevant information and a large heterogeneity in target populations, outcome measures and intervention content [71].

Moreover, it is necessary to establish the need for tailoring the intervention to specific patients. And, if tailoring is necessary, the degree of tailoring and ways to effectively apply

tailoring needs to be further investigated. In this light, finding the most optimal outcome measures for tailored interventions is needed. Combining generic and specific outcome measures may be a solution, when both are kept within the boundaries that are acceptable to patients to fill out, for example integrating goal attainment scaling [72, 73] as part of the outcome measures. Tailoring could be achieved by a therapist, but may in the future also be (partially) achieved by technological advances that allow for fine-tuning to specific patient characteristics [74]. For example, if a technological system has sufficient information on patient characteristics the system could automatically select the matching treatment characteristics.

Therapist guidance warrants further investigation. The developed instrument to measure internet-specific elements should be further investigated, tested on a larger scale and the relation to adherence and outcome is yet to be established. In this study, psychologists had at least a Masters degree in psychology. Other studies have shown guidance can also be offered by other groups, including for example patient peers, or students in psychology [71, 74]. However, in view of the high tailoring aspects of the internet-delivered therapy in the current study, this might be not sufficient for this type of tailored CBT. As the costs of the therapist is a large portion of the intervention costs, the time spent by the therapist and the degree to which a specialized therapist is needed, could be studied for example by comparing interventions with different levels of therapist support.

Clinical trials are a challenge to conduct, e.g. in the light of patient recruitment, using the right instruments in terms of both outcomes and patient comfort, and in maintaining the same intervention for an extended period of time. It has been argued that the gold standard of randomized controlled trials may not be feasible in the era of fast technological developments. Other research methods are increasingly being used such as stepped wedge

designs, case studies with repeated measurements or individual patient trajectory analysis [75, 76], and may be a useful addition to traditional methods such as the randomized controlled trial presented in this thesis. Yet, internet-based questionnaires and technological advances may also be useful in improving recruitment and assessments. When taking new pathways in research, as well as in clinical practice, a balance needs to be sought between conducting sound research and clinical practice, and keeping up with possibilities that may significantly improve patients' quality of life.

To conclude

In this thesis, several aspects of ICBT for patients with chronic somatic conditions have been outlined. The studies in this thesis are an addition to the current literature on ICBT and a step forward in studying patient preferences and therapeutic guidance during these interventions. Tailored guided ICBT is a promising step towards improving psychological outcomes for patients with RA with elevated levels of distress and ultimately improving their quality of life despite living with a chronic condition.

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